The

RENAL ORIGIN

of

HYPERTENSION

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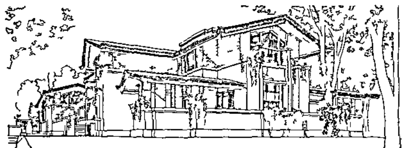
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The RENAL ORIGIN *of* HYPERTENSION

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PREFACE

In recent years in several books (1-4) the present state of our knowledge of human and experimental hypertension has been described and discussed in great detail. It is legitimate therefore to question why a written lecture on this subject should be published at this time. My first impulse is to apologize for making this contribution which is incomplete and in great part repetitious but on second thought I have considered that it may prove of some value to those whose interest is not sufficient to induce them to read the original papers or who do not have the time to devote to the reading of books on this topic. To me the whole subject continues to be fascinating and I consider that it should be of great interest to all students of medicine and even to laymen. The justification for this statement is that (1) the death rate from arteriosclerotic disease of the brain heart and kidneys associated with the symptom of hypertension continues to be very high (about four times that of cancer) (2) fully 25% of deaths at least in males over 50 years of age is associated with the existence of this condition (3) treatment has done but little to reduce these figures (4) there are no known methods of prevention and (5) the initiating cause or causes of the two associated conditions arteriosclerosis and hypertension are still obscure or unknown. It is my ardent hope therefore that the advances in our knowledge of the pathogenesis of human hypertension based on the investigations of experimental renal hypertension may yet lead to the prevention and cure of this condition which takes such a large toll of human lives.

CONTENTS

The

RENAL ORIGIN

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INTRODUCTION

Not infrequently medical historians find it difficult or even impossible to assign the origin of an idea to a single person. Although Richard Bright knew nothing about hypertension because in his time blood pressure in man had not yet been measured, yet there is little doubt that to him should go the credit for the basic idea that hypertension may be of renal origin. Although Bright did not differentiate clearly between the various types of renal disease and although he knew nothing of the important entity which is now called *essential hypertension*, yet he did make the important observation that in cases of cardiac hypertrophy not obviously due to intrinsic cardiac disease or extrinsic vascular abnormality there is found almost without exception some disease of the kidneys. Basing himself upon this observation with the intuition of a great clinician who was also greatly interested in pathology, he speculated that the increased weight of the heart (hypertrophy) might be related to the disease of the kidneys. Indeed he went so far as to suggest that a chemical alteration of the blood resulting from the renal disease was probably the immediate cause of the cardiac hypertrophy by effecting an increased action of the heart and, what is more important, by inducing what amounts to increased peripheral vascular resistance to the onflow of blood. The latter idea is nothing short of remarkable for the time, for if there is one thing that appears to be definitely settled about the basic mechanism of the state of hypertension in man it is the existence of a state of increased peripheral vascular resistance. The specific parts played by arteriosclerosis and by generalized spasm of the arterioles and the primary or secondary relationship of these changes to the hypertension still constitute a controversial subject. What is not yet settled also, despite all the work that has been done on the subject, is the question of the renal origin of the type of hypertension that is now usually referred to as *essential*, or *primary*.

In a normal animal direct determinations of blood pressure had been made by Stephen Hales in 1733, one hundred years before Bright, but in man measurements of blood pressure were not made until the end of the nineteenth century. Although on the basis of other indirect methods, particularly palpation of the pulse, pulse

tracings and other bloodless methods the existence of a state of increased vascular tension in man had been recognized yet it was not until the development by Riva Rocci of a method to determine blood pressure (really bursting tension) by a pneumatic cuff and a mercury manometer that the existence of elevated blood pressure in man was fully recognized its significance appreciated and the study of its pathogenesis undertaken

After the discovery of the existence of elevated blood pressure in man it was realized at once that the enlargement of the heart observed by Bright was a direct consequence of the hypertension and the problem switched at once to the pathogenesis of the increased peripheral vascular resistance What confused the problem was the previous discovery by Johnson and by Gull and Sutton of organic disease of the small arteries and arterioles which consisted of thickening of the walls and reduction in the size of the lumen an obviously possible organic cause of increased peripheral vascular resistance The direct result of this was that one group of investigators a minority group contended with Johnson that the renal disease was the cause of the hypertension the diffuse vascular disease and the hypertrophy of the heart while the other group asserted with the followers of Gull and Sutton that the hypertension and consequent cardiac hypertrophy were the direct result of the increased peripheral vascular resistance caused by the diffuse organic disease which only incidentally involved the kidneys This division of opinion has survived up to the present time with one addition namely that the primary phenomenon is increased peripheral vascular resistance due to vasospasm (neurogenic or endocrinogenic) which results in increased peripheral resistance and hypertension and that all the organic changes vascular and cardiac are secondary to the hypertension

In more recent times it has been recognized that primary renal disease may be associated with hypertension and that a causative relationship between the two conditions may exist In such cases the presence of the renal disease is recognized usually by reason of renal excretory functional abnormalities which result from pathologic changes in the kidneys These include polycystic disease of the kidneys glomerulonephritis (acute and chronic) bilateral obstruction of ureters from any cause bilateral chronic pyelonephritis and other conditions which involve considerable reduction of renal parenchyma and in which disturbance of excretory function usually

occurs After the recognition of essential hypertension doubt was cast upon the frequency with which renal disease might be considered the cause of the initiation of the elevated blood pressure As a matter of fact renal disease characterized by disturbance of renal excretory function has always been excluded from the definition of essential hypertension Dalton and Nuzum believe however that the critical statistical analysis of the data on renal excretory function in cases of essential hypertension in man does show in most cases some impairment of ability to concentrate urine and to excrete phenolsulfonphthalein The fact that renal excretory functional abnormality frequently cannot be demonstrated for many years after the onset of hypertension and even throughout the entire course of the disease convinced many investigators that most cases of hypertension are not on a renal basis As a result hyperepinephrinemia abnormal pituitary function neurogenic stimuli affecting the vasomotor mechanism and diminution of the sensitivity of the carotid sinus are some of the conditions that have been considered at various times the cause of this type of hypertension

Most students and investigators of the subject of essential hypertension are now in complete agreement that cardiac output, and the volume and viscosity of the blood are within the limits of normal in well established essential hypertension It is therefore generally agreed that with few exceptions the ultimate cause of the elevated blood pressure is increased peripheral vascular resistance Although there is still some division of opinion about whether the increased vascular resistance is ever on an organic basis yet most investigators are of the view that peripheral vasospasm is the physiological basis for the phenomenon That the organic changes in the peripheral blood vessels especially the arterioles are ever so widespread as to be a purely mechanical cause of hypertension is not supported by the anatomical findings of pathologists Also physiologists and clinicians have shown that the peripheral arterioles exhibit normal physiological responses to physical and chemical stimuli for example the normal vasodilator response of the vessels of the forearm and hand to heat and reactive hyperemia (Prinzmetal Pickering) and the normal depressor response to an intravenous injection of 0 1 mg of histamine acid phosphate (Pickering and Kissin) The process of vasospasm therefore can be adduced as the cause of the increased peripheral resistance

The one man who kept the idea of the possible renal origin of some forms of human hypertension alive was Volhard who believed that in pale (malignant) hypertension at least the pathologic change in the kidney plays an important part in the development of the elevated blood pressure He even sought but failed to find a vasoconstrictor substance in the blood of patients with this condition Although there are those who still deny that the kidneys ever play a primary part in the initiation of hypertension yet it is now quite generally admitted that some forms of renal disease may in some way be the cause of the hypertension What is not generally admitted is that essential hypertension especially the benign phase the type of hypertension that is usually associated with widespread arteriolar sclerosis and especially with nephrosclerosis but without accompanying excretory functional abnormality is of renal origin The arguments usually given against the renal origin of essential hypertension are (1) the frequent discovery of elevated blood pressure long before there is any recognizable sign of renal excretory insufficiency (2) the absence of any recognizable signs of renal excretory insufficiency throughout the entire course of the hypertension in a large percentage of cases and (3) the failure to find at autopsy significant intrarenal vascular disease in an occasional case of essential hypertension

Experimental proof for the view that the kidneys play a primary part in the development of the increased peripheral vascular resistance and consequent hypertension had been sought in a variety of ways before our own experiments on this subject began in 1928

Production of Experimental Renal Hypertension By Various Methods

Unilateral and bilateral nephrectomy had been tried but had not resulted in hypertension in the rabbit cat and dog (Mosler 1912 Bichman 1916 Cash 1926) Most experiments of a similar nature that have been performed up to the present time have been in agreement with the early results (Harrison Blalock and Mason 1936) but recently Grollman has asserted that hypertension may develop in dogs and rats as a result of unilateral nephrectomy

Reduction of the amount of functioning renal tissue by partial resection of each kidney had been reported as causing slight hypertension in the rabbit cat and dog (Cash 1924) and since 1928 sev

eral investigators have noted the development of considerable hypertension in the rat but not in the dog as the result of this procedure (Ferris and Hynes 1931 Chanutin and Ferris 1932 Wood and Ethridge 1933) In the light of our own studies on the dog and because only the rat gave a pronounced effect it is suggested that the cause of the elevation of the blood pressure in these animals was the hemodynamic disturbance in the small remnant of the kidneys caused by the scarring from the surgical operation

The effect of a nephrotoxic substance such as uranium had been tried on rabbits by Beckmann (1925) and Dominguez (1928) but elevation of blood pressure was not produced consistently Since then other investigators using the same and other nephrotoxic agents have obtained contradictory results Lead salts sodium and potassium oxalate mercury bismuth and streptococcus toxin are among the other substances that have given negative or equivocal results The direct injection of trypsin into the renal artery (Freedman and Katz, 1938) failed to produce persistent hypertension It has been shown that nephrotoxic heterologous antiserum to rabbit renal substance produces glomerulonephritis and renal excretory insufficiency accompanied by slight elevation of blood pressure (Masugi 1934) This has also been accomplished in the rat (Smadel 1937) and confirmed for the rabbit but Corcoran and Page (1941) failed to observe elevation of the blood pressure in the dog with glomerulonephritis produced by a nephrotoxic serum

Irradiation with roentgen rays of the kidneys of dogs caused moderate elevation of blood pressure but impairment of renal excretory function was an invariable accompaniment (Hartman and collaborators 1929) This was confirmed later by Page (1936) for the dog but Hermann Dechard and Erhard (1941) failed to observe indirect evidence (cardiac hypertrophy) of hypertension in the rabbit as a result of irradiation of the kidneys

Occlusion of one or both ureters was first tried in 1929 by Hartwich who observed some elevation of blood pressure associated with fatal uremia in the dog as a result of bilateral occlusion of the ureters This result has been fully confirmed but most investigators have reported failure to produce hypertension as a result of unilateral occlusion of a ureter Constriction of one ureter with contralateral nephrectomy also did not result in hypertension in the dog (Eichelberger 1938) In the light of our own experiments

it appears probable that occlusion of a ureter may produce a hemodynamic disturbance similar to but not as pronounced as the effect of constriction of the main renal artery

Compression of the kidneys by an oncometer had been tried in 1909 by Alwens who reported slight immediate elevation of blood pressure in some brief experiments in cats More recently a similar effect on the kidney of a persistent type has been produced by Page and collaborators (1939) by the envelopment of the kidneys in cellophane or silk The same effect has been obtained in rats and dogs (Greenwood Nassim and Taylor 1939 Hermann Jourdan and Vial 1940) by means of collodion painted on the surface of the kidneys and also by compression of the kidneys by means of a tape tied in a spiral form around the kidney (Grollman 1944) These methods are supposed to act by direct compression of the kidney substance or by the compression and resultant ischemia caused by the thick perirenal scar which results from the perinephritis induced by the foreign material The main drawback of the method is the frequent accompaniment of renal excretory functional disturbance and even fatal uremia

Embolism by the direct injection of various substances (liquid paraffine Berlin blue charcoal) directly into the renal artery of cats and dogs had given consistently negative results (Senator 1911 Cash 1924) More recently however Maegraith and McClean (1938) reported the development of hypertension in the rabbit as the result of the injection of kieselguhr into the main renal artery of rabbits The same substance failed to produce high blood pressure in the dog (Crestman and Blalock 1939)

Passive hyperemia of one kidney produced by the constriction of the main renal vein had been reported by Pedersen in 1927 as causing a transient elevation of blood pressure in the dog This has been confirmed by Braun Menendez (1933) Dicker (1937) and Friedberg (1944) It did not prove to be a method for the production of persistent hypertension on a renal basis because bilateral constriction of the main renal veins invariably resulted in fatal uremia

Permanent occlusion of the main renal artery, vein and ureter of both kidneys had failed to cause hypertension in the dog (Cash 1926) Although Loesch (1933) did report hypertension in the dog as the result of intermittent occlusion of all the structures of the renal pedicle yet there is reason to believe that the hypertension developed

only when constriction of some of these structures became permanent as the result of scarring

Arteriovenous anastomosis had not been tried before 1928 In 1939 Weber and Rumold produced hypertension accompanied by uremia in the dog by arteriovenous anastomosis of one kidney and contralateral nephrectomy This did not prove to be a method for the production of persistent hypertension

Occlusion of the main renal arteries had been tried in 1905 by Katzenstein who reported an immediate slight rise of blood pressure probably of reflex origin in some brief experiments Cash in 1926 reported a rise of blood pressure in dogs that survived occlusion of both main renal arteries for several days but died in uremia This result has been confirmed since then by many other investigators including ourselves Although the animals develop elevated blood pressure yet they die in uremia so this is not a good method for the production of persistent hypertension Although the animals die in uremia as in the case of bilateral nephrectomy yet different from the latter elevation of blood pressure does occur This is understandable in the light of our own experiments on the basis that although a state of profound renal ischemia exists yet blood flow through the kidney does not cease altogether and a pressor substance of renal origin may enter the circulation by way of the main renal vein or the lymphatics

Ligation of branches of the main renal artery gave contradictory results and the hypertension when it did occur did not persist (Janeway 1913 Marl 1928 Hartwich 1930 Friedmann and Wachsmuth 1930, Wolf and Heinsen 1935 Konzett and Unna 1937 Verney and Vogt 1938) Occlusion of the main artery of only one kidney also resulted in slight temporary elevation of blood pressure in dogs but all of these experiments were published after 1929 (Friedmann and Wachsmuth 1930 Hartwich 1932 Winternitz and collaborators 1940) It is not a method for the production of persistent hypertension

Constriction of the main renal artery had also been tried before 1928 but Katzenstein (1905) observed only slight elevation probably of reflex origin in a brief experiment while Bridgman and Hirose (1916) reported no elevation of blood pressure in dogs as a result of the same procedure

The administration of sterols (cholesterol) had also been tried

many times (Fahr 1912 vanLeersum 1912 Schonheimer 1924 Shapiro and Seecoff 1925 and Lowenthal 1926) but always with the idea of producing generalized arteriosclerosis and consequent hypertension as a result of generalized increased peripheral vascular resistance and not with the intention of proving the renal origin of hypertension The results obtained were contradictory Even the administration of vitamin D (Appelrot 1933) (Handovsky 1937) which did result in elevation of blood pressure was based upon the same idea of generalized arteriosclerosis as a cause of hypertension but the pronounced nephrotoxic effects drew attention to the possible renal origin of this type of hypertension In recent years it has been reported (Ham 1940 Grollman Harrison and Williams 1940 Marzek Novak and Reed 1942 and Selye and collaborators 1942) that desoxycorticosterone induces the development of hypertension and Selye has asserted that the hypertension is associated with the development of nephrosclerosis in the rat and therefore may be of renal origin

Some of the experiments summarized above merely proved what is generally accepted even for man, namely the renal origin of hypertension associated with renal excretory insufficiency as a result of great reduction of renal parenchyma from any cause or obstruction of the urinary passages However those experiments that were designed to prove the renal origin of essential hypertension failed in most instances because (1) they were brief experiments in most of which no elevation of blood pressure was demonstrated or the hypertension was fleeting and probably of nervous reflex origin, (2) contradictory results were obtained by different investigators using similar methods (3) when hypertension did result the experimental conditions did not reproduce the anatomical or what is more important the physiological state of the kidneys in *benign* essential hypertension and (4) the hypertension did not persist or was accompanied by renal excretory insufficiency with or without uremia

This was the state of the whole problem when our own investigations of the subject began in 1928 The working hypotheses of these studies were as follows (1) the part possibly played by the kidney in initiating so called essential hypertension should be susceptible of experimental investigation (2) if vascular disease limited to the kidneys, or any other pathologic process capable of producing a similar intrarenal hemodynamic disturbance be the primary factor

in the initiation of essential hypertension then the production of the counterpart of the physiological effect of such vascular or other renal disease no matter how it may be accomplished should result in the development of hypertension (3) renal excretory functional disturbance should not be a necessary accompaniment of the experimental hypertension (4) The directive thought was that since stenosing sclerosis of the smaller arteries and arterioles is the most common renal lesion associated with essential hypertension then if the consequent disturbance of renal hemodynamics is the cause of the hypertension the reproduction of this condition by any means should also result in the development of elevated blood pressure It was considered that the fulfillment of all these conditions would answer the requirements of the definition of essential hypertension and signify the experimental reproduction of this condition

Since there was no known way at that time of reproducing the significant anatomical abnormality namely arterial and arteriolar sclerosis localized to the kidneys it was considered that the best way to reproduce the counterpart of the probable physiological effects of this intrarenal organic vascular disease would be to constrict the main renal arteries Since the main effects of preglomerular arterial and arteriolar disease of the kidney are probably reduction of intraglomerular capillary pressure and reduction of blood flow to the functioning components of the kidney it was considered that these two effects might be reproduced by the constriction of the main renal artery by means of a clamp It should be appreciated at once that the method decided upon was a compromise that it does not mean that it was considered that stenosing arteriosclerosis of the main renal artery is a frequent finding in cases of human essential hypertension and that the application of the clamp was considered an exact reproduction of the *anatomical* state of the kidney in essential hypertension This is emphasized here and will be again because some authors and investigators have been guilty of this misinterpretation

PRODUCTION OF EXPERIMENTAL RENAL HYPERTENSION BY CONSTRICTION OF MAIN RENAL ARTERY

For the purpose of constricting the main renal artery it became necessary first to devise a clamp which would fulfill the following requirements (1) it would induce little or no tissue reaction so that it might be left permanently on the artery (2) it would permit

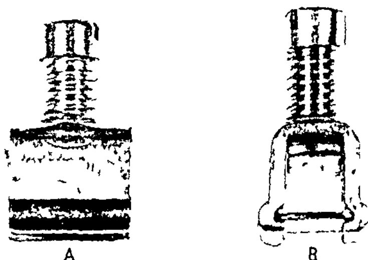
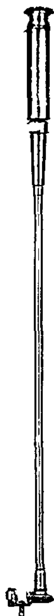


Fig 1 Clamps for constriction of renal arteries Clamp with movable and removable plates and double acting screw Ordinary type (A) Side view (B) Movable plate in open position (After Goldblatt *Am J Clin Path* 10 40 1940)

Fig Clamp holder for ordinary type clamp (Fig 1) (A) Screw driver to depress or elevate the movable plate (B) The clamp holder with the clamp in it without the removable plate in the position ready to receive the renal artery (C) The same instrument with the holder of the clamp holder turned over by the depression of the spring in the handle of the clamp (D) The clamp holder with the clamp in position so that the screw of the clamp is accessible to the screw driver for the depression of the removable plate and compression of the renal artery (E) The removable plate held in the jaws of this special instrument It is with this special instrument that the removable plate is inserted into the clamp in the clamp holder (After Goldblatt *Am J Clin Path* 10 40 1940)



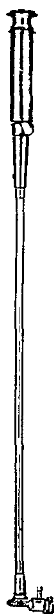
A



B



C



D



E

constriction of the artery to any desired extent (3) it would permit increase or decrease of constriction of the artery and (4) it would be removable later without injury to the artery All these requirements were fulfilled by the clamp made of pure silver which was finally devised for the purpose (Fig 1)

Special instruments were also devised to aid in the application of the clamp They are not necessary but they facilitate and expedite the application of the clamp (Fig 2) The clamp the instruments and the surgical procedure have been described in detail in several publications including *Medical Physics*

A clamp made of tantalum or of some of the other metals which induce little tissue reaction might be even more desirable than silver if they could be worked for the purpose

EFFECT ON BLOOD PRESSURE OF MODERATE CONSTRICTION OF THE MAIN ARTERY OF ONLY ONE KIDNEY

An early and unexpected observation was elevation of the blood pressure as the result of constriction of only one main renal artery. There was no immediate rise of blood pressure but within a period of 24 to 72 hours after the constriction of the main artery of only one kidney the blood pressure became elevated. In the dog the hypertension usually lasted not longer than six weeks and only

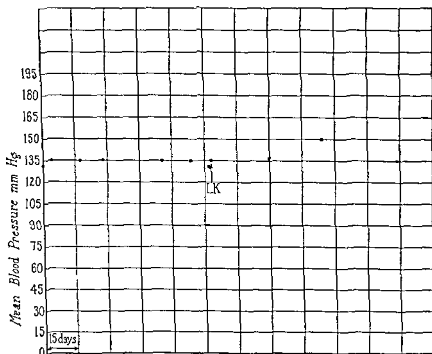


Fig. 3 Dog 3 35 male chow young Initial weight 17.4 Kg LK = left main renal artery moderately constricted —— = Mean blood pressure mm Hg direct method femoral artery This shows that it took about 48 hours for the blood pressure to become significantly elevated that the maximum was reached in about a week that it remained elevated at the maximum level for about two weeks and that it returned to the normal preoperative level in about six weeks after the maximum had been reached (After Goldblatt The *Harvey Lectures* 1937 38)

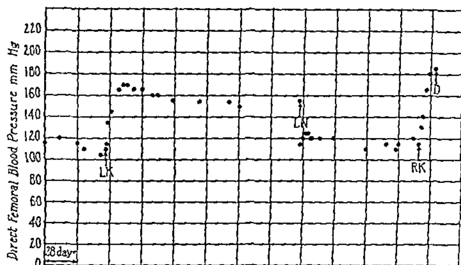


Fig 4 Goat 3 female age about 1 year LK left main renal artery was moderately constricted The direct mean femoral blood pressure remained considerably elevated for six months LN the left kidney was excised and within 24 hours the blood pressure returned to normal and remained at this level RK the right main renal artery was greatly constricted The blood pressure became re elevated but the animal developed uremia and died (D) Terminally B U N (blood urea nitrogen) 134 mg Cr 5 8 mg CO combining power 40 5 volumes per 100 cc (After Goldblatt Kahn and Lewis *J Exper Med* 7 97 303 1943)

occasionally as long as six months Usually the pressure reached a maximum elevation in about one week remained elevated at that level for another week and then gradually returned to normal in 4 to 6 weeks (Fig 3) It was found later that in the goat the sheep and the rat unilateral constriction of a main renal artery resulted in hypertension that usually persisted for months (Fig 4)

A significant early observation by the author and others was the effect of the removal of the kidney with renal artery constricted This resulted in prompt (12 24 hours) return of the blood pressure to normal (Fig 4 5) These results drew attention to the possibility that human hypertension may also be caused by unilateral renal disease and more important that the removal of the diseased kidney provided the contralateral kidney is normal might also result in the return of the blood pressure to normal This will be referred to again under the heading of surgical treatment

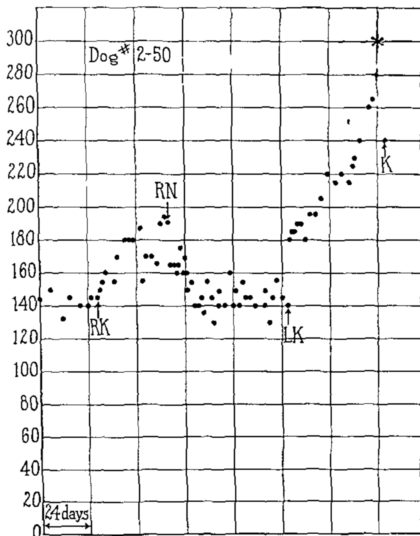


Fig 5 Removal of an ischemic kidney and production of ischemia in the remaining kidney Mean blood pressure in mm Hg (RK) right main renal artery moderately constricted (RN) right nephrectomy at a time when the mean blood pressure was elevated resulted in its prompt return to normal (LK) *great constriction of* main renal artery of left kidney This was followed by very high elevation of mean blood pressure the mean blood pressure at this time was more than 300 mm Hg (K) killed (After Goldblatt *Ann Int Med* 11 69 1937)

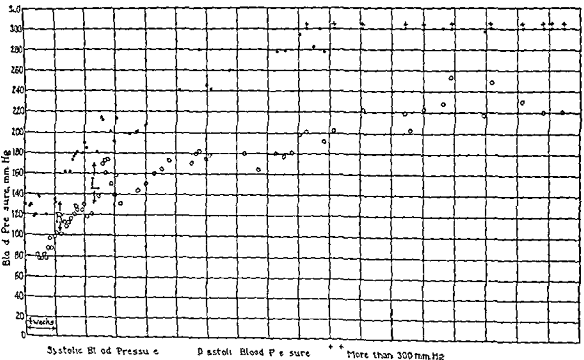


Fig. 8 Monkey 5 Female macaque age about 1 year at beginning of experiment Weight 4 kilos at beginning and three kilos at end of experiment R main artery right kidney greatly constricted but not occluded L main artery left kidney greatly constricted but not occluded [illegible] Systolic blood pressure [illegible] Diastolic blood pressure + More than 300 mm Hg Both systolic and diastolic pressures became elevated and remained elevated for 16 months after the clamping of the right renal artery During the period of acute illness which lasted nine days and proved fatal no determinations of blood pressure were made The elevation of both systolic and diastolic pressure shows that this was true hypertension (After [illegible] J Exper Med 65 671 675 1937)

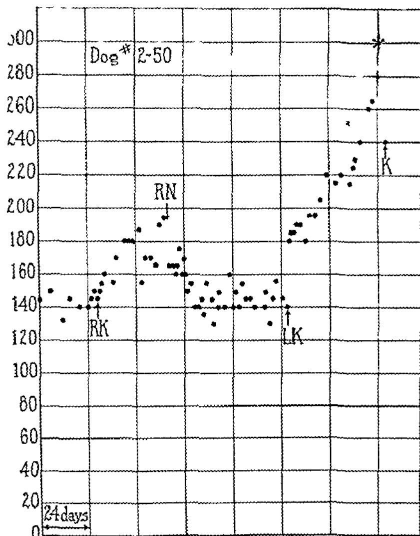


Fig. 5. Removal of an ischemic kidney and production of ischemia in the remaining kidney. Mean blood pressure in mm Hg. (RK) right main renal artery moderately constricted. (RN) right nephrectomy at a time when the mean blood pressure was elevated resulted in its prompt return to normal. (LK) great constriction of main renal artery of left kidney. This was followed by very high elevation of mean blood pressure ... the mean blood pressure at this time was more than 00 mm Hg. (K) killed. (After Goldblatt, *Ann. Int. Med.*, 11 69 193 .)

I FFLCT ON BLOOD PRESSURL OI MODLRATL CON STRICTION OF BOTH MAIN RLNAL ARTFRILS THL BLNIGN PHASL OF LXPLRIMLNTAL RENAL HYPLRTLNSION

In order to make the hypertension persist it was found necessary to constrict the main artery of both kidneys (Fig 6) or to constrict the main artery of one kidney and remove the other kidney (Fig 7) Constriction of both main renal arteries at the same time resulted in a definite rise of blood pressure usually within 24 hours with the maximum rise occurring in two weeks or even longer In most experiments an interval of a week or longer was allowed between the clamping of the two main renal arteries (Fig 6) The removal of the

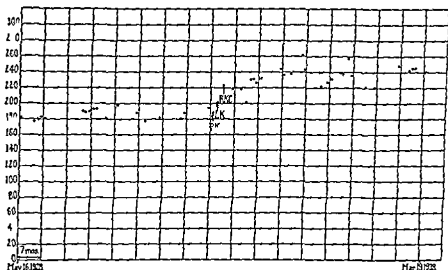


Fig 6 Blackie short haired mongrel female age about 1 year in 19 8 Initial weight 14 Kg RK = moderate constriction of right main renal artery LK = moderate constriction of left main renal artery RKC = occlusion of right main renal artery = systolic blood pressure mm Hg determined by the vanLeersum carotid loop method This shows that the blood pressure remained elevated for about 5 years after the constriction of both main renal arteries At no time did this animal show any significant disturbance of renal excretory function as determined by various type of clearance and by the chemical composition of the blood (After Goldblatt The Harvey Lectures 193 38)

contralateral kidney for the purpose of making the hypertension persist was also performed as a rule in not less than a week after the constriction of the main artery of one kidney (Fig 7) By both procedures many investigators have now succeeded in producing persistent hypertension in dogs monkeys rabbits rats cats sheep and goats In some of the dogs persistent elevation of blood pressure

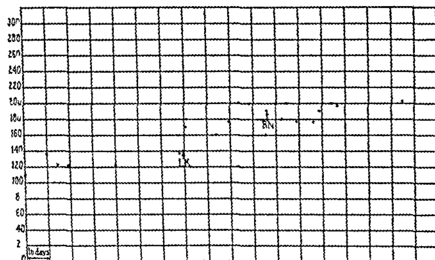


Fig 7 Dog 3 14 male bulldog young Initial weight 11 Kg LK = great constriction of left main renal artery RN = right nephrectomy —— = mean blood pressure mm Hg direct method femoral artery This shows that the blood pressure may become elevated and remain elevated for several weeks as the result of constriction of only one main renal artery and that the hypertension may become persistent as a result of the subsequent removal of the contralateral kidney (After Goldblatt *The Harvey Lectures* 1937 38)

has been observed for more than 6 years That this is true hypertension has been shown by the demonstration that both systolic and diastolic pressures are elevated (Fig 8)

Immediately after the application of the clamp there is considerable reduction of the blood flow through such kidneys and the blood pressure in the part of the renal artery distal to the clamp is definitely decreased Whether these two effects persist indefinitely has not yet been established

In many of the animals with persistent hypertension due to moderate constriction of both main renal arteries there was little or no decrease of renal excretory function detectable by any of the methods

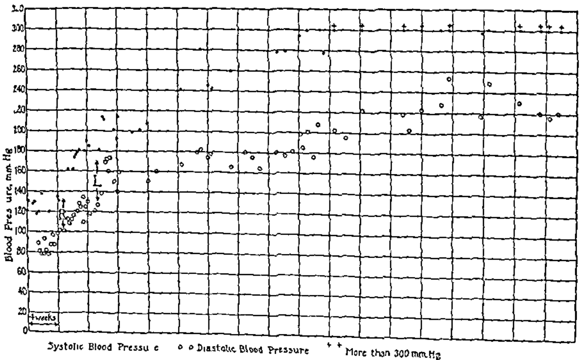


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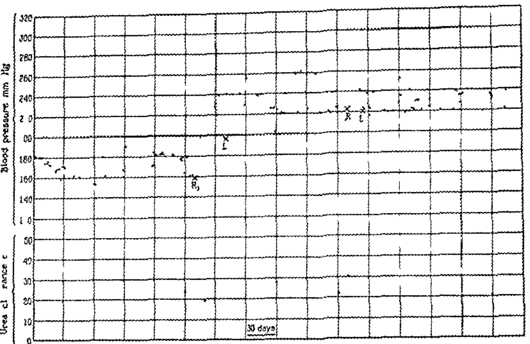


Fig 9 Dog 5 9 Initial weight 17 4 kg R = moderate constriction of right main renal artery L = moderate constriction of left main renal artery R and L = constriction of right and left main renal arteries increased to very great = systolic blood pressure determined by the Van Leersum carotid loop method This illustrates the persistent hypertension without any associated disturbance of renal excretory function as determined by the urea clearance At no time in the life of this animal was there any increase in the values for the non protein nitrogen blood urea or creatinine in the blood (After Goldblatt Lynch Hanzal and Summerville *J Exper Med* 59 347 349 1934)

used in clinical medicine (Fig 9) It was shown therefore experimentally that merely by disturbance of the intrarenal hemodynamics hypertension was produced which although obviously of renal origin nevertheless had no accompanying disturbance of renal excretory function Thus the most important of the working hypotheses was satisfied by the results of these experiments The direct application of this observation to man is perhaps not justifiable but it does offer experimental evidence for the view that essential human hypertension usually associated with intrarenal arterio and arteriolo sclerosis but without impairment of renal excretory function may also be of renal origin In recent years as the result of the work of many in

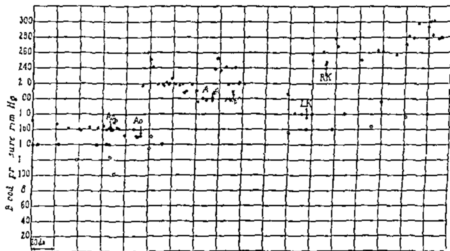


Fig 10 Doberman pinscher female young 18 Kg Ao abdominal aorta just below the origin of both main renal arteries greatly constricted by a clamp Ao abdominal aorta just below the origin of both main renal arteries greatly constricted by a clamp Ao c abdominal aorta above the main renal arteries occluded by tightening the clamp Ao c abdominal aorta below the main renal arteries occluded by tightening the clamp LK left main renal artery greatly constricted by a clamp RK right main renal artery greatly constricted by a clamp The figures for blood pressure which appear as solid black circles represent the carotid systolic pressure determined by the vanLeersum carotid loop method The figures which appear as open circles represent femoral mean pressure determined by the direct method This shows that the constriction of the aorta below the origin of the main renal arteries has no significant effect on the blood pressure in the upper part of the body whereas constriction of the aorta above the origin of both main renal arteries results in a definite rise of pressure which as in the case of constriction of both main renal arteries begins in about 24 hours after the operation Note that even in the femoral artery after recovery from the initial fall of blood pressure the final pressure was eventually higher than normal (After Goldblatt Kahn and Hanzal *J Exper Med* 69 649-674 1939)

vestigators much evidence has accumulated to favor this view This will be discussed in a later part of this monograph

It was also shown that constriction of the aorta just above the site of origin of both main renal arteries results in elevation of the

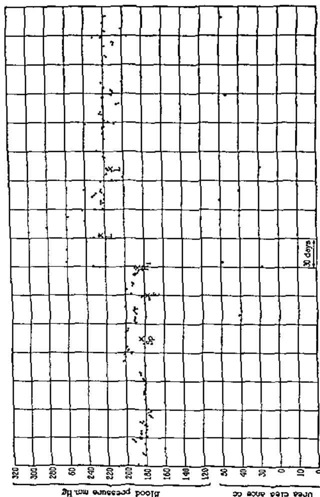


Fig 11 Dog 6 0 Initial weight 18 kg SP = almost complete constriction of main splenic artery F = great constriction of both femoral arteries immediately below Poupart's ligament R and L = moderate constriction of right and left main renal arteries respectively L = constriction of left main renal artery increased to almost complete This control study shows that constriction of the splenic and femoral arteries in the same animal had no significant effect on the blood pressure and that the hypertension developed only when the renal arteries were constricted This also illustrates the fact that there was no significant disturbance of renal excretory function throughout the entire experimental period even after the renal arteries were constricted (After Goldblatt Lynch Hanzal and Summerville *J Exper Med* 59 347 3/9 1934)

blood pressure whereas constriction of the aorta immediately below the origin of the renal arteries is not followed by the development of elevated blood pressure (Fig 10) It is of special interest in connection with the pathogenesis of hypertension due to constriction of the main renal arteries that when the aorta above the origin of both main renal arteries was constricted although the mean blood pressure

in the femoral arteries was lower than normal for a time yet eventually it became definitely elevated although not as much as in the upper part of the body In this connection Steele s observation that in cases of coarctation of the aorta in man the diastolic arterial pressure is frequently as elevated below the site of constriction as above it is of great interest A reduced effective renal blood flow and normal glomerular filtration rate have also been reported in such cases by Friedman Selzer and Rosenblum on the basis of indirect evidence (diodrast and inulin clearances) This is similar to the conditions which obtain in essential human hypertension Other control studies were also carried out In the same animal the splenic artery and both femoral arteries were constricted This caused no elevation of the blood pressure (Fig 11)

For reasons that are difficult to understand there are those who minimize the importance of these experiments because in human hypertension the main renal artery is not commonly stenotic and they consider therefore that the experimental constriction of the main renal artery does not reproduce exactly the state of the human kidney in essential hypertension This is admitted of course although there are authors like Yule and Blackman who have drawn attention to the frequent existence of stenosing arteriosclerosis of one or both main renal arteries in association with human hypertension However what is forgotten or ignored by some writers is that constriction of the main renal artery was an expedient resorted to experimentally because it was the only method available whereby to induce a disturbance of the circulation of the kidney that might possibly simulate the most probable effects not only of stenosis of a main renal artery but also of intrarenal stenosing arterial and arteriolar sclerosis To regard the experimental type of hypertension as not exactly like human essential hypertension because the main renal artery in human beings with hypertension is not frequently stenotic is to misunderstand the whole problem and the main purpose of the experimental procedures which were used for the production of experimental renal hypertension The recognition of this probable similarity is necessary to a proper understanding and evaluation of the contributions made by the great variety of studies carried out on animals with experimental renal hypertension

In some of the animals with both main renal arteries moderately constricted after a period of weeks or months the blood pressure re

turned to a lower level or even to the original normal level To re elevate the pressure it was often sufficient merely to increase the constriction of one or both main renal arteries (Fig 9) In other animals the examination of the kidneys showed that the potential accessory circulation to the periphery of the kidney had become strikingly prominent with large arterial vessels entering the cortex of the kidney from the various surrounding organs and structures Decapsulation and enclosure of one or both kidneys in a fishskin condom frequently resulted in a re elevation of the blood pressure which often persisted This type of membrane did not induce the development of the thick hull of connective tissue around the kidney which is induced by wrapping cellophane collodion or silk around a kidney but it did reduce the accessory circulation to the kidney and it was thought that this induced the re elevation of the blood pressure Cellophane collodion and silk membranes (Page and others) have been wrapped around kidneys and elevation of blood pressure has been observed to develop weeks or months after the application of these membranes The elevation of the blood pressure in these animals has been considered as due to the perinephritis and the compression of the renal substance by the thick hull of connective tissue which develops around the kidneys That actual compression of the kidney occurs has not been proved In fact there is no proof that the mechanism of the elevated blood pressure is not due to the scar tissue which also develops around the renal pedicle with constriction of the artery vein and ureter of the kidney Two indications of this are the passive hyperemia (venous obstruction) and hydronephrosis (ureteral obstruction) in some degree which are almost invariably observed at autopsy in such kidneys This is a matter which should be settled In any event it is believed that the pathogenesis of the hypertension in such cases is similar to that which results from constriction of the main renal arteries The main drawback of the method is that impairment of renal function is an almost invariable accompaniment of the hypertension and fatal uremia (the malignant phase) is a common outcome

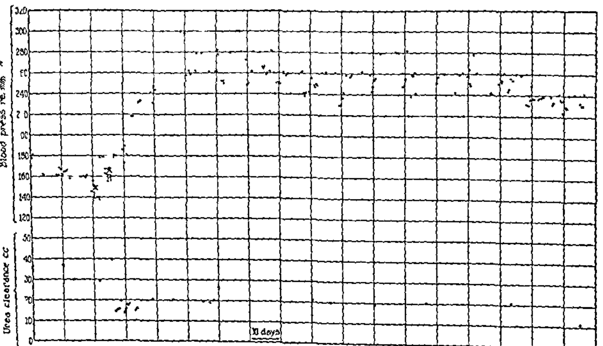


Fig 12 Dog 3 8 female Initial weight 11 2 kg L = great constriction of left main renal artery R = great constriction of right main renal artery Note the persistent *reduction of urea clearance to about 50% of normal* throughout the life of this animal This was the only sign of impairment of renal excretory function At no time however was there any accumulation of non protein nitrogen products in the blood (After Goldblatt Lynch Hanzal and Summerville *J Exper Med* 59 347 379 1934)

EFFECT ON BLOOD PRESSURE OF GREAT CONSTRICTION OF BOTH MAIN RENAL ARTERIES THE MALIGNANT PHASE OF EXPERIMENTAL RENAL HYPERTENSION

If both main renal arteries are greatly constricted from the beginning or in some cases if moderate constriction is practiced at first and great constriction later elevation of blood pressure accompanied by variable degrees of impaired renal excretory function is the result (Fig 12) If the renal arteries are greatly constricted

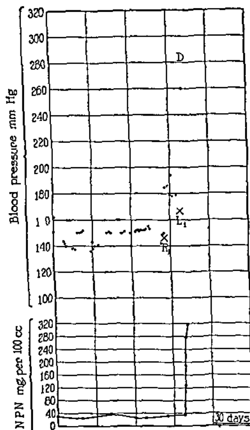


Fig 13 Dog 8 7 female Initial weight 14 0 kg R = almost complete constriction of right main renal artery L = almost complete constriction of left main renal artery D = Died The animal died in uremia as illustrated by the great accumulation of NPN in the blood Creatinine and blood urea nitrogen were also greatly increased and the urea clearance was greatly decreased Anatomically this animal showed both in the gross and microscopically the typical arteriolar lesions of the malignant phase (See Plate 1) After Goldblatt Lynch Hanzal and Summerville *J Exper Med* 59 347 379 1934)

from the beginning, and especially if both renal arteries are occluded fatal uremia results The same effect can be produced by excessive constriction of one main renal artery with contralateral nephrectomy or contralateral ureteral occlusion In those animals that develop great impairment of renal excretory function along with the hypertension fatal convulsive uremia occurs (Fig 13) and at autopsy pathologic changes are found in the small arteries and arterioles which resemble those observed in the malignant phase of essential hypertension More will be said about these changes under the heading of pathologic changes

Thus hypertension resembling both the benign and the malignant phases of essential hypertension has been produced experimentally in animals merely by varying the degree of constriction of the main renal arteries and the consequent alteration in the intrarenal circulation The exact nature of this disturbance of intrarenal hemodynamics has not yet been determined More will be said later about the evidence that has accumulated to indicate that the benign and malignant phases of essential hypertension in man may also be primarily of renal origin



PATHOLOGIC CHANGES IN THE ORGANS OF ANIMALS WITH PERSISTENT HYPERTENSION

Within the kidney the pathologic changes which result from constriction of the main renal artery are directly dependent upon the degree of constriction of this vessel In the benign phase that is in hypertensive animals with moderate constriction of the main renal arteries and without accompanying renal excretory insufficiency the kidneys may show little if any significant gross or microscopic ab normalities detectable by the usual methods In the early stages changes in the mitochondria of the proximal convoluted tubules may be found even in those kidneys in which later no obvious anatomical changes are detectable Pathologic changes in the structure of the kidneys are therefore not necessary for the determination of the benign phase of experimental hypertension produced by constriction of the main renal artery

Sellurt has shown that in dogs a considerable lowering of the systemic blood pressure alone may result in a disproportionately low renal blood flow with striking physiologic evidence of tubular damage yet without correspondingly striking histological alterations in the kidney depending upon the duration and degree of the anoxia This may mean that intracellular changes not detectable by the usual methods have occurred with consequent alteration in intracellular enzymes and other substances

In some hypertensive animals after several months one of the kidneys may be found atrophic even though significant diminution of renal excretory function had not occurred In such animals the other kidney is usually hypertrophic and both in the gross and microscopically essentially normal In some of these small kidneys there is little or no interstitial fibrosis and the reduced size of the organ is due mainly to disappearance of glomeruli and of cortical tubules as well as shrinkage of the tubules which have no distinct lumen and which are lined by greatly altered epithelium in which signs of regeneration (mitoses and hyperchromatic nuclei) are com

mon in the lining epithelial cells This is the so called *endocrine kidney* which Selye has produced in the left kidney of rats by constriction of the aorta between the origin of both main renal arteries Whether in such kidneys there is actual transformation of an exocrine to an endocrine type of cell and the part that these cells play in the origin of the hypertension which develops remain to be determined

In animals in the malignant phase especially when both main renal arteries are greatly constricted at the same time profound parenchymatous degeneration or diffuse necrosis with or without hemorrhage may occur in both kidneys

In the benign phase in dogs even after 6 years of persistent hypertension no significant pathologic changes have been observed in the aorta or in the large or small arteries The only changes that have been detected in the vascular system of such animals have been slight to moderate hypertrophy of the heart and thickening of the media of the large and small arteries due to hypertrophy and hyperplasia of the muscle fibers These experiments therefore afford no proof for the view that hypertension by itself is a sufficient condition for the production of generalized true simple arterial or arteriolar *sclerosis*

In the malignant phase in animals even when it terminates fatally

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Plate 1 Arterial Lesions in Malignant Hypertension →

Part 1 Arteriole in submucosa of large intestine Beginning subendothelial deposit of hyalin Endothelium well preserved *Hematoxylin and Eosin* × 265

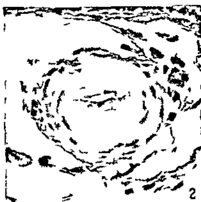
Part 2 Arteriole in submucosa of stomach Obliterative hyalinization of intima endothelium still recognizable but nuclei reduced in number and pyknotic Hematoxylin and Eosin × 430

Part 3 Arteriole in submucosa of small intestine Lumen completely obliterated by accumulation of hyalin containing a few pyknotic nuclei Hematoxylin and Eosin × 430 Parts 1 2 and 3 are from an animal that lived for one month after great constriction of both main renal arteries Renal excretory function was greatly impaired

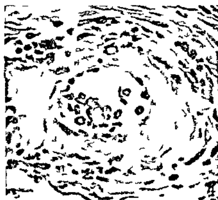
Part 4 Arteriole in submucosa of stomach Portion of entire thickness of wall necrotic Normal thickness of wall and lumen natural size Hematoxylin and Eosin × 375

Part 5 Arteriole cut longitudinally in submucosa and mucosa of large intestine *Partly hyalinized partly necrotic* with extravasated blood around it A portion of the same arteriole in the submucosa immediately proximal to the part included in this figure was entirely normal Hematoxylin and Eosin × 255 (After Goldblatt, *J Exper Med* 67 809 1938) Parts 4 and 5 are from an animal that lived for one week after great constriction of both main renal arteries The animal developed convulsive uremia









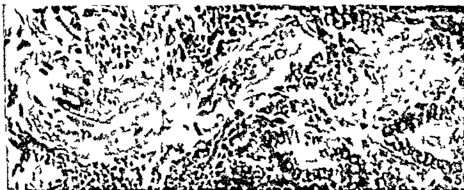


PLATE I

in as little as 48 to 72 hours the most profound changes have been observed *in the blood vessels of the dog monkey rabbit rat* sheep and goat The changes are similar to those seen in the terminal phase of human malignant hypertension In the gross the condition is manifested by petechiae in the gastro intestinal tract gall bladder urinary bladder pancreas adrenals brain pericardium and myocardium Microscopically in the aorta there is only interstitial edema mainly of the media but the wall of small arteries and arterioles in those organs in which the petechiae occur is the seat of necrosis and fibrinoid degeneration with or without vascular and perivascular inflammation characterized by the exudation of polymorphonuclear leukocytes *and some lymphoid cells* The necrotizing and inflammatory changes in the arterioles are indistinguishable from those observed in the terminal phase of malignant human hypertension (Plate 1) There is however one significant difference from the malignant phase in human beings the vascular lesions do not occur in the blood vessels of the kidneys beyond the site of constriction of the main renal artery Even intrarenal necrotizing arteriolar lesions have been produced Great constriction of the main artery of one kidney and ligation of the ureter of the other kidney resulted in hypertension accompanied by renal insufficiency (Goldblatt and Kahn) The arteriolar *lesions of the malignant phase developed in the kidney with ureter* occluded in which intrarenal arterial tension was increased but not in the kidney with the main renal artery constricted in which the intrarenal arterial tension was undoubtedly low

Pathogenesis of arteriolar necrosis Of the mode of development of the degenerative necrotizing and inflammatory lesions of the arterioles which are found in many internal organs in the malignant phase of experimental renal *hypertension nothing definite is known* These vascular lesions are indistinguishable from those found in human beings in the malignant phase of essential hypertension and are not to be confused with simple arteriolosclerosis observed in the benign phase of human essential hypertension *In animals the arteriolar* lesions are usually more severe and more widespread than in man This may merely indicate a greater susceptibility of the vascular system of animals to these changes As in human beings with malignant hypertension some organs especially the lungs skin and skeletal muscles rarely show these lesions The fact that the kidneys fail to show *these lesions* may afford a clue to their mode of development

The intravascular pressure within the kidney beyond the site of constriction of the main renal artery is low In man even the intra renal vascular pressure is usually high because obliterative sclerosis of the main renal artery does not usually accompany the condition As a matter of fact it has never been shown even in malignant human hypertension that the arterioles which correspond to a larger arterial branch which is the seat of stenosing arteriosclerosis ever become necrotic It may be that only those arterioles become necrotic that are subjected to a high bursting tension as well as to the effects of the chemical substance or substances in the blood which result from the renal damage In some cases of malignant hypertension in man necrosis of the renal arterioles does not occur These may be cases in which there is widespread stenosing arteriosclerosis of the larger intrarenal arteries or of the main renal artery with or without arteriolosclerosis within the kidney It seems therefore that a combination of increased vascular tension and the effect of a chemical substance of renal origin the result of interference with circulation of the kidney are necessary conditions for the production of arteriolar necrosis and the associated hemorrhages That elevated intravascular pressure alone is not a sufficient condition for the production of the necrotizing arteriolar lesion is demonstrated by the absence of these lesions in the organs of animals that have had pronounced hypertension for many years without accompanying significant disturbance of renal excretory function or in the kidneys of animals with experimental neurogenic hypertension This indicates that intense vasospasm alone is not a determinant of these lesions That the chemical factors alone is not sufficient for the production of the arteriolar lesions is demonstrated by the fact that bilaterally nephrectomized animals with profound azotemia but without hypertension do not develop the necrotizing lesions of the arterioles and the associated petechiae That the lesions of the arterioles are not due to ischemic necrosis is of course shown by their absence from the ischemic kidneys of the animals and their presence in organs in which there is no obvious ischemia What the exact nature of the chemical substance or substances is that plays the important part in the production of the anatomical lesions has not yet been elucidated by the investigations of renal hypertension that have been performed up to the present Winternitz and his collaborators have been able to produce lesions of a similar nature by repeated injections of an extract of kidneys But this does not prove that these chemical sub

stances, by themselves have the ability to produce these lesions because the extract also produced a considerable elevation of blood pressure so that a combination of the effect of the hypertension and of the chemical factor cannot be excluded Although renin was used in these experiments yet there is no proof that the chemical substance responsible for the lesions was renin or is renin in hypertensive animals for the renin used by Winternitz and collaborators was not pure

The inflammatory changes around the blood vessels are probably only a reaction to the degeneration and necrosis of the walls of the arterioles but it cannot be denied that they may be caused by the same agent that produces the necrosis By repeated intravenous injections of tyramine some investigators have produced lesions of arterioles which they consider similar to those of the malignant phase but there is certainly no good reason for the belief that tyramine is responsible for the lesions of the malignant phase of hypertension

Wilson and Byrom and others have asserted that they observed the characteristic malignant arteriolar lesions in one kidney in rats with hypertension due to constriction of the main renal artery of the contralateral kidney We have not been able to confirm these observations in dogs rabbits monkeys sheep or goats with hypertension due to constriction of one main renal artery The conclusion reached by Wilson and Byrom confirmed by others that hypertension by itself is able to cause the characteristic malignant arteriolar lesions in the rat with hypertension due to constriction of only one main renal artery has not been substantiated in the experiments on any other animals and is probably based on the erroneous assumption that the contralateral kidney was normal All the glomerular and interstitial inflammatory lesions within the otherwise supposedly normal kidney, described by these authors have been observed by us in the kidneys of rats with normal blood pressure The best explanation of the changes in the arterioles of the contralateral kidney observed by Wilson and Byrom and the others is probably that they were unaware of the frequent existence of hydronephrosis or pyelonephritis in one or both kidneys of adult rats and that by constriction of only one main renal artery they were really dealing in some of these rats with bilateral renal disease The possibility still remains that the rat in this respect differs from all other animals

Other changes in experimental renal hypertension It was

shown early that the hypertension which results from constriction of the main renal arteries involves both the systolic and the diastolic pressures and the elevation of these has been demonstrated in a variety of ways In experimental renal hypertension the pulse rate remains unchanged and no significant alteration in the output of blood from the heart has been observed in the hypertensive animals The volume of the blood in hypertensive dogs shows no significant variations from the normal The pressure in the lesser circulation (the main pulmonary artery) is also within the limits of normal which indicates that the pulmonic vessels are not affected by peripheral vascular constriction in this type of hypertension In the blood apart from the retention of nitrogenous products in the animals in the malignant phase no significant changes have been observed The pH of the blood remains within the limits of normal in animals in the benign phase (Muller and Nickel) No significant alterations in the lipid and protein content of plasma have been noted but Page did report a slight increase of free cholesterol at the expense of the esterified fraction No special significance has been attached to this change In animals that exhibit retention of nitrogenous products accumulation of the guanidine compounds also occurs but since there is no accumulation of this product in the benign phase no special significance has been attached to the presence of this pressor substance in the blood even in the malignant phase A redistribution of the water content of skeletal muscles of dogs with experimental renal hypertension has been found (Eichelberger) This merely indicates some extracellular edema which occurs mostly in the malignant phase

As concerns the physiological reactions in hypertensive animals it is of interest that the carotid sinus and cardioaortic nerves are not able to effect a lowering of the blood pressure to normal in animals with main renal artery constricted There is some difference of opinion about the effect of occlusion of the common carotid arteries in animals with experimental renal hypertension Some authors have found a greater rise of blood pressure in such animals than in those with normal blood pressure We have found that the excision of both carotid sinuses did not alter the development of hypertension produced by renal ischemia and that the level of blood pressure reached by such animals was no different from that of animals with carotid sinuses intact It seems therefore that the regulatory system of the blood pres

sure functions actively in experimental renal hypertension and that it probably acts normally *although at a high level It has been found* that animals with experimental renal hypertension react in hypersensitive fashion to injections of adrenalin tyramine and pitressin but no one has suggested that these substances play any part in the origin of the elevated blood pressure In fact because the injection of cocaine causes no fall of blood pressure in hypertensive dogs Robbers and *Westenhoeffer have concluded that tyramine cannot be the cause* of experimental renal hypertension It has also been shown that the dog's reaction to the cold pressor test is the same after the development of hypertension as it was in the pre hypertensive state Many investigators have found that the presence of an infection causes a fall of the blood pressure which returns to its initial level after the infection has disappeared The type of infection which produces the most profound and the most lasting effect is distemper The prolonged effect on the blood pressure is probably due to the slow recovery of animals from this type of infection This is a lead which probably deserves more attention than it has received Similar effects can be obtained by the injection of bacteria or bacterial products for example typhoid vaccine injected intravenously will produce a temporary significant fall of blood pressure in animals with experimental renal hypertension as it does also in human beings with essential hypertension Whether or not this effect is produced by the dilatation of afferent arterioles and improvement of circulation of the kidneys or by relaxation of efferent glomerular arterioles and decrease of intraglomerular pressure has not been established

PATHOGENESIS (MECHANISM OF DEVELOPMENT) OF EXPERIMENTAL RENAL HYPERTENSION

The production of the counterpart of the benign and malignant phases of human hypertension has made possible the investigation of the probable pathogenesis of the high blood pressure even in man. Since the original publication of the production of experimental renal hypertension the pathogenesis of this type of hypertension has been discussed in many publications which have dealt mainly with the possible application of the observations on animals to the problem of the mechanism of production of human essential hypertension.

It is obviously impossible to solve a problem of this kind by the study of patients clinically or by examination of specimens of tissues obtained at autopsy. Progress in the acquisition of our knowledge of the pathogenesis of human hypertension has therefore been delayed because in human beings it is rarely if ever possible to study the patient before and after the development of the elevated blood pressure.

The arteriolar sclerosis of the kidneys which has been reported by many authors (Fishberg, Bell and Clawson, Moritz and Oldt) as an almost invariable finding in cases of human essential hypertension at autopsy has been interpreted by some as proof for the view that the hypertension comes first and produces the renal vascular disease. The possible causal relationship between the two conditions could conceivably be investigated by the examination of biopsy specimens of kidney obtained from the same individuals at intervals before and after the development of hypertension. Since there is no way of telling with any degree of certainty which persons will develop hypertension, such a study of human beings is not feasible. An approach to this problem has been made by the examination of biopsy specimens of kidneys in cases of established human hypertension after the condition had been in existence for a variable length of time (Castleman and Smithwick). This study has not led to a solution of the problem for obvious reasons and the conclusion of the

authors that the results of their investigation show that the vascular disease is caused by the hypertension is hardly justifiable

In a series of patients with hypertension that had existed for variable periods biopsy specimens of the kidneys were examined for vascular disease (Castleman and Smithwick) In these small specimens in which at best only a few cross sections of independent arterioles could be observed the changes were classified arbitrarily *from 0 to ++++* on the basis of hyaline thickening of the wall and stenosis of the lumen Despite the views and conclusions of the *authors it is an interesting and indeed an extraordinary fact that* some vascular abnormality was found in about 90% of the specimens and that in about 50% *it was from moderate to severe From* the study of such small specimens it is obviously impossible to tell whether the vascular disease is more or less pronounced in the remainder of the kidney It is hazardous therefore to extrapolate from the evaluation of such minute specimens of heterogeneous tissue to an estimate of the average condition of a single constituent the arteriole of the entire organ Even if the appearance of a few arterioles could possibly give some estimate of the average change in similar vessels of the remainder of the kidney yet it can give no idea of the state *of the larger intrarenal vessels or of the hemodynamic state of the* entire kidney The larger intrarenal arteries are rarely included in such biopsy specimens because the specimens are taken from the periphery of the cortex It should be obvious that stenosis of one large intrarenal artery could account for great hemodynamic disturbance in a large mass of kidney substance supplied by many arterioles that are not themselves diseased In human nephrosclerosis stenosing arteriosclerosis of large intrarenal vessels is a common accompaniment of the arteriolar sclerosis The possible contribution of such obliterative sclerosis of the *large intrarenal arteries and even* of the main renal artery to the disturbance of intrarenal hemo*dynamics has been underestimated Indeed Blackman has shown how common it is to find in hypertensive patients at autopsy* some degree of stenosis even of the main renal artery At no time of course has it been asserted that stenosis of the main renal artery unilateral or bilateral is a common cause of or even a frequent finding in, human essential hypertension It is difficult therefore to understand why some authors should make a special point of emphasizing that in many hypertensive patients in whom pronounced sten

osis of one or both main renal arteries was found there was also present significant intrarenal arteriolar sclerosis This is to be expected and it is probable that in most of these cases the intrarenal disease developed first and determined the initial elevation of the blood pressure However the possible part played by the obliterative sclerosis of the main renal artery cannot be denied

The possible mechanisms involved in the elevation of the blood pressure are (1) afferent nervous stimuli from the nerve endings in the kidneys to the vasomotor center or sympathetic ganglia with resultant generalized vasoconstriction and consequent elevation of blood pressure (2) afferent stimuli from the kidneys with resultant output of an increased amount of some known internal secretion which produces vasoconstriction either by central or peripheral action (3) the entrance into the circulation of a primary pressor substance of renal origin or the new formation of a pressor substance as a result of the interaction of a renal substance with substances already present in the blood Teleologic considerations are mentioned only to be discarded because they are not susceptible of experimental proof

Neurogenic mechanism The possible part played by various portions of the nervous system was investigated first It was soon shown that experimental renal hypertension is not caused by a nervous reflex from the kidney affecting the vasomotor mechanism of the body Renal denervation (Fig 14) bilateral supradiaphragmatic excision of splanchnic nerves and lower dorsal sympathetic ganglia (Figs 15 16) subdiaphragmatic splanchnicectomy with excision of the celiac and upper lumbar ganglia bilateral section of the anterior nerve roots from the 6th dorsal to the second lumbar inclusive (Fig 17) pithing with destruction of the entire spinal cord and complete sympathectomy including denervation of the heart (Fig 18) neither prevent nor abolish the hypertension which results from constriction of the main renal artery Even under anesthesia (pentothal) experimental renal hypertension persists whereas known neurogenic hypertension disappears These results eliminated the idea that a nervous reflex originating in the kidney is the cause of the experimental renal hypertension and indicated that a humoral mechanism was probably the cause There are those like Ogden however who concede that the renal humoral pressor mechanism initiates experimental renal hypertension but who believe that this is superseded

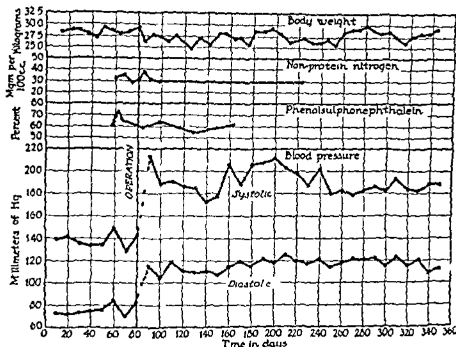


Fig 14 Effect of denervation of the kidneys and constriction of the renal arteries In the case of the blood pressure each point represents an average of the readings taken over a period of ten days Note that renal denervation does not prevent the production of hypertension (After Collins *Am J Physiol* 116 616 1936)

later by a neurogenic mechanism mediated through the sympathetic nervous system This view has not been established by any means and much more investigation is definitely indicated

Endocrinogenic mechanism The French school is especially committed to the view that in human essential hypertension hyperpinephrinemia is a highly probable cause Although there are those who *still cling to the idea that essential hypertension is primarily* endocrinogenic and due to some disturbance of the hypophysis yet the experiments on animals have failed to lend support to this view

Complete hypophysectomy does not permanently lower the blood pressure of a dog with experimental renal hypertension and does not prevent the development of this type of hypertension (Fig 19) There is no proof that the activity of the posterior lobe of the pituitary is changed in any way in experimental renal hypertension The amount of the antidiuretic principle in the urine remains unchanged in experi

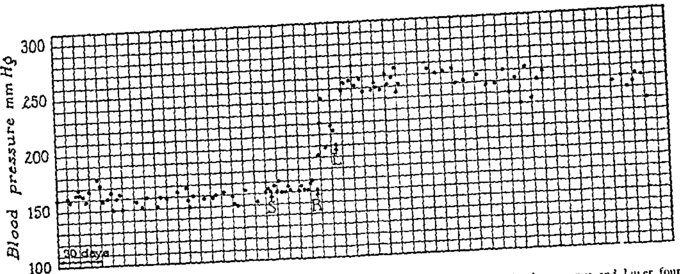


Fig. 15 Dog 35 female Initial weight ? Kg. S = bilateral excision of thoracic portion of splanchnic nerves and lower four dorsal sympathetic ganglia R = moderate constriction of right main renal artery L = moderate constriction of left main renal artery The blood pressure was unaffected by the excision of the nerves but rose in the usual way after constriction of the main renal arteries and remained elevated after constriction of the main arteries Systolic blood pressure determined by the van Leersum carotid loop method (After Goldblatt Cross and Hanzal J Exper Med 65 33 41 1937)

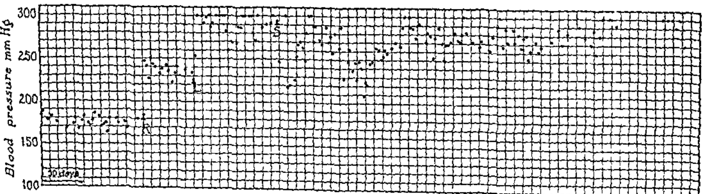


Fig 16 Dog 2 10 male Initial weight 0 Kg R = moderate constriction of right main renal artery L = moderate constriction of left main renal artery S = bilateral excision of the intrathoracic portion of splanchnic nerves and lower four dorsal sympathetic ganglia For a period of about three months following this operation the blood pressure was very irregular and at times dropped considerably but never reached normal levels Later the blood pressure became re elevated and remained as high as it was before excision of the splanchnic nerves Systolic blood pressure determined by the van Leersum carotid loop method (After Goldblatt Gross and Hanzal *J Exper Med* 65 233 241 1937)

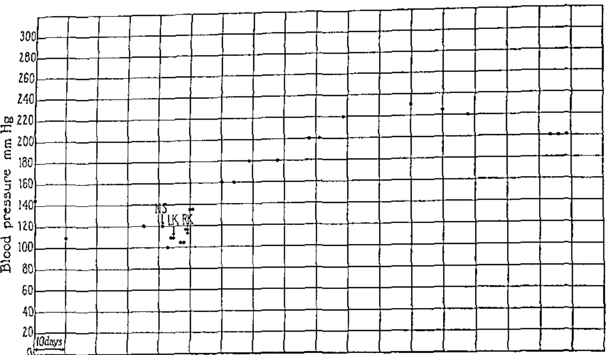


Fig 17 Dog 3 09 female Initial weight 10 2 kg NS = section of anterior spinal nerve roots from sixth dorsal to second lumbar inclusive LK = moderate constriction of right main renal artery The mean femoral blood pressure became elevated in the usual way after the constriction of both the main renal arteries (After Goldblatt and Wartman *J Exper Med* 66 527 534 1937)

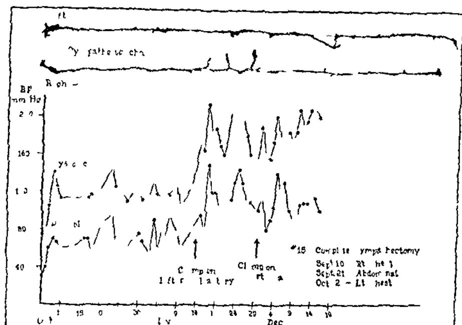


Fig 18 Effect of sympathectomy on development of renal hypertension *Effect of constriction of the renal arteries on the systolic and diastolic pressure of a dog in which both paravertebral sympathetic chains were removed from the stellate ganglion to the pelvic chain The unbroken sympathetic chains removed are shown in the upper part of the chart Note that sympathectomy does not prevent the production of hypertension* (After Freeman and Page *Am Heart J* 14 405 193)

mental renal hypertension but during dehydration it is increased in both normal and hypertensive animals Excision of the posterior pituitary does not interfere with the development of or lower experimental renal hypertension in the rabbit

Thyroidectomy gonadectomy and pancreatectomy have no significant effect in preventing or lowering experimental renal hypertension in the dog

The only endocrine organ which may possibly play a significant even if only a secondary part in experimental renal hypertension is the adrenal Even this conclusion has been contested (Rogoff) In the earliest study of experimental renal hypertension it was shown that the medulla of the adrenal plays no part in the origin or maintenance of the elevated blood pressure (Fig 20) There is however some indication that the adrenal cortex may play a secondary part in this type of hypertension although there are those who do not

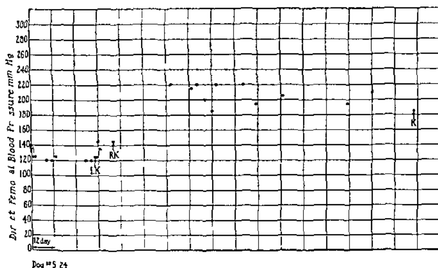


Fig 19 The effect of complete hypophysectomy on the development of hypertension due to constriction of both main renal arteries Dog 5 24 male middle aged chow weight 11 Kg H = complete hypophysectomy LK = moderate permanent constriction of left main renal artery RK = moderate permanent constriction of right main renal artery K = killed Complete hypophysectomy had no significant permanent effect on the level of blood pressure of the normal animal and did not interfere with the development of hypertension due to constriction of both main renal arteries (After Goldblatt Braden Kahn and Hoyt *J Mt Sinai Hosp* VIII Jan Feb 194)

concede even this The complete excision of both adrenals in dogs interferes with the development of hypertension due to constriction of the main renal arteries unless adequate supportive and substitution therapy is given (Figs 21 22) When only two fifths of the cortex of one adrenal is present there is no interference with the development of experimental renal hypertension in the dog (Fig 23) When both adrenals of a hypertensive animal are removed the blood pressure falls promptly to normal (Fig 24) It will be shown in the discussion of the humoral mechanism that the possible mode of action of the cortical hormone is to influence the production of the pseudoglobulin in the blood which acts as the substrate for the activity of renin to form the pressor substance hypertensin

Recently Victor reported the production of hypertension in dogs by ligation of the hilar vein and of grossly visible arteries and veins at either the superior or the inferior pole of only one adrenal It is evident of course that nerve fibers must have been included in the polar ligature although Victor does not make special mention of this

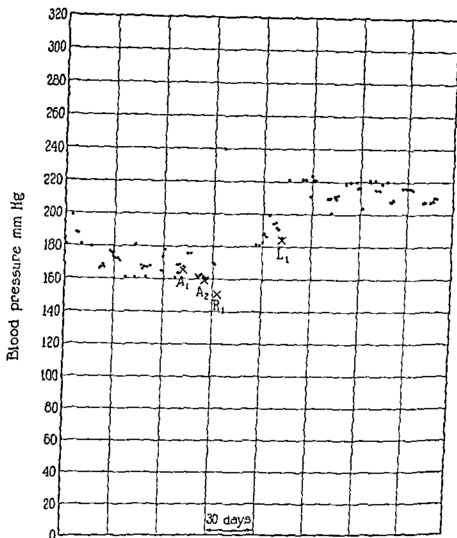


Fig 0 The effect of removal of one adrenal and destruction of the medulla of the other adrenal on the development of hypertension due to constriction of both main renal arteries Dog 8 9 Initial weight 13 6 Kg A = excision of right adrenal A = destruction of medulla and denervation of left adrenal Section of left major and minor splanchnic nerves R and L = moderate constriction of right and left main renal arteries, respectively The elimination of the medulla of both adrenals had no significant effect on the development of hypertension due to constriction of both main renal blood arteries Systolic blood pressure determined by the van Leersum carotid loop method (After Goldblatt Lynch Hanzal and Summerville *J Exper Med* 59 347 3 9 1934)

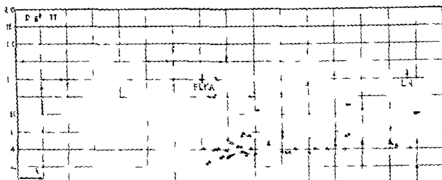


Fig 21 The effect of bilateral adrenalectomy on the development of hypertension due to constriction of both main renal arteries = mean blood pressure mm Hg • = non protein nitrogen mg per 100 cc = CO combining power volumes per 100 cc RLKA = bilateral adrenalectomy and both main renal arteries moderately constricted LN = left nephrectomy + = intravenous adrenal cortical extract begun = adrenal cortical extract discontinued During the entire period following the bilateral adrenalectomy the animal received by stomach tube in two equal doses (9 00 a m and 4 00 p m) a total of 0 75 gm per kg of body weight of sodium chloride and 0 25 gm per kg of body weight of sodium bicarbonate At no time during the four months of survival did the animal show elevated blood pressure Several times when cortical extract was discontinued the blood pressure fell to very low level K = killed (After Goldblatt *Ann Int Med* *11* 1937)

No explanation of or speculation about the mechanism of the hypertension was given by Victor We have repeated these experiments in 6 dogs but have failed to confirm the result In one of these dogs the operation was performed by Dr Victor himself but this animal too failed to develop hypertension More work will have to be done on this subject before any final conclusion can be reached about the significance of this contribution

A theory which deserves careful consideration is that of Selye (5) (General adaptation syndrome) who believes that various nonspecific types of stress acting by unknown pathways on the anterior hypophysis produce an increase of the adrenal corticotrophic hormone which in turn causes the adrenal cortex to produce an increased amount of desoxycorticosterone like substances (corticoid hormone) which affect the *target* organs one of which is the kidney with resultant intrarenal arteriosclerosis and hypertension He believes that the anterior hypophyseal substance and the adrenal cortical substance may act independently or synergistically upon the kidney and that the adrenal cortical hormone may even stimulate the anterior hypo

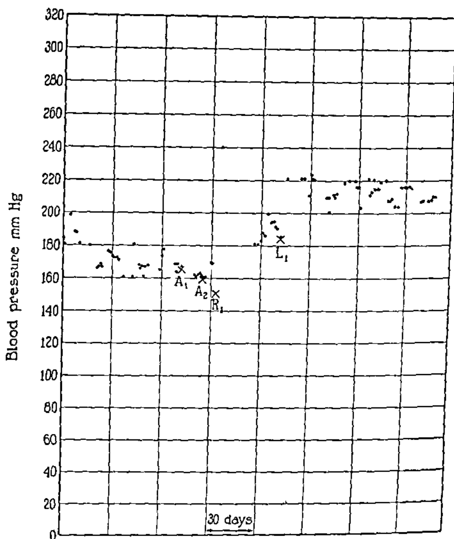


Fig 20 The effect of removal of one adrenal and destruction of the medulla of the other adrenal on the development of hypertension due to constriction of both main renal arteries Dog 8 9 Initial weight 13 6 Kg A = excision of right adrenal A = destruction of medulla and denervation of left adrenal Section of left major and minor splanchnic nerves R and L = moderate constriction of right and left main renal arteries respectively The elimination of the medulla of both adrenal had no significant effect on the development of hypertension due to constriction of both main renal blood arteries Systolic blood pressure determined by the van Leersum carotid loop method (After Goldblatt Lynch Hanzal and Summerville *J Exper Med* 59 347 3 9 1934)

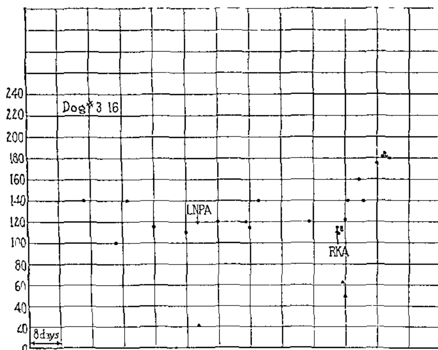


Fig 23 Dog 3 16 female 14 0 Kg The effect of a remnant of adrenal cortex on the development of experimental renal hypertension = mean blood pressure mm Hg ▲ = non protein nitrogen mg per 100 cc plasma LNPA = left nephrectomy and partial adrenalectomy The medulla was destroyed About two fifths of the cortex was left RKA = right adrenalectomy and right main renal artery greatly constricted = sodium chloride (0 75 gm per Kg of body weight) and sodium citrate (0 25 gm per Kg of body weight) were given by stomach tube from this time on = sodium chloride and sodium citrate discontinued No cortical extract was given at any time The blood pressure rose moderately following the constriction of the renal artery and remained elevated when supportive treatment was discontinued This shows that the presence of a small remnant of adrenal cortex adequate to help to keep the animal alive was sufficient to permit the development of hypertension after the constriction of the main renal artery of the only kidney (After Goldblatt *Ann Int Med* 11 69 103 1937)

physis to produce a direct effect upon the kidney It is of interest that according to this author the kidney still plays a central part in the determination of the elevated blood pressure and that the hypertension may be the result of the recognized humoral mechanism of

one month during which the dog received substitution as well as supportive treatment Whenever the intravenous cortical extract was discontinued (—) the blood pressure gradually fell to a level below normal When cortical extract was begun again (+) the blood pressure gradually rose but did not reach the previous hypertensive level D = died of pneumonia (After Goldblatt *Ann Int Med* 11 69 103 1937)

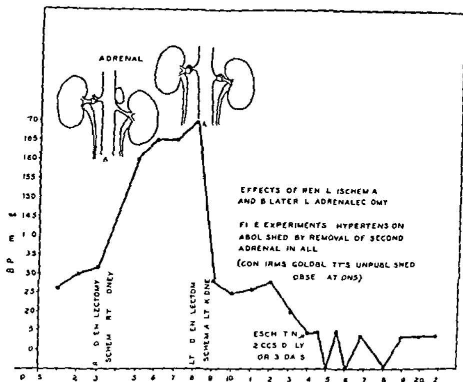


Fig. 24 Effect on blood pressure of bilateral adrenalectomy and renal ischemia Effect on the blood pressure of removal of both adrenals combined with bilateral renal ischemia Observe the rapid fall of blood pressure following removal of the second adrenal gland (After Blalock and Levy *Ann Surg* 106 8 6 193)

experimental renal hypertension In addition this theory offers a possible explanation for the origin of the intrarenal arteriosclerosis so frequently found in association with the hypertension The experimental work which Selye and collaborators have published on this subject has dealt less with hypertension than with the production of intrarenal arteriosclerosis which they accomplished by the administration of large doses of desoxycorticosterone acetate mainly to unilaterally nephrectomized rats but also to other animals fed on a high sodium diet Much more work on this subject is necessary before the part that the hypophysis and adrenal may play in the origin of both vascular disease and hypertension can be considered as definitely established

THE HUMORAL MECHANISM OF EXPERIMENTAL RENAL HYPERTENSION

The earliest indication that a humoral mechanism might be responsible for the elevated blood pressure in experimental renal hypertension was the effect of tying off the renal veins in dogs with the main renal arteries constricted adequately to produce hypertension Although these animals developed uremia and died in from two to seven days yet at no time did they show any elevation of the blood pressure (Fig 25) Tying off of the renal veins of hypertensive animals also resulted in a prompt fall of the blood pressure The gradual elimination of a possible primary part played by the nervous and endocrine systems also stimulated the search for a probable humoral mechanism of renal origin which might be responsible for the elevation of the blood pressure in this type of hypertension and possibly also in human essential hypertension In fact most of the recent contributions to this subject have dealt with the humoral mechanism About this mechanism there are now two distinct views (1) That a kidney with main renal artery constricted or the seat of any pathologic conditions which bring about a disturbance of the circulation similar to constriction of the main renal artery may be the source of a substance which when it enters the circulation raises the blood pressure (2) that the normal kidney is ordinarily the source of a substance the action of which prevents hypertension and that it is the absence destruction or neutralization of this substance which results in the elevated blood pressure (Grollman) Most of the evidence presented to date favors the former view

In the first place it was shown that interference with the blood supply to any other organ but the kidney does not result in either temporary or permanent elevation of the blood pressure Constriction of the celiac axis and superior mesenteric artery of the femoral and splenic arteries (Fig 11) and of the aorta below the origin of both main renal arteries (Fig 10) does not produce a rise of blood pressure in animals It has certainly been shown that azotemia alone

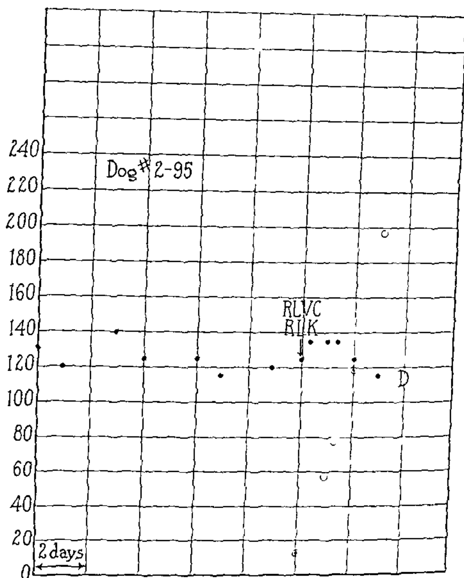


Fig. 25 The effect *of occlusion of the main renal veins on the development of* hypertension due to moderate constriction of both main renal arteries Dog 2 95 female 16.4 kg • = mean blood pressure mm Hg ○ = blood urea nitrogen mg per *100 cc RLVC = both main renal veins occluded RLK = both main renal* arteries greatly constricted The animal died in uremia but the blood pressure did not become significantly elevated The failure *of* the blood pressure to rise was interpreted as due to interference with the entrance *of a pressor producing substance from* the kidney into the systemic blood (After Goldblatt *Ann Int Med 11* 69 103 1937)

is not a sufficient condition for the elevation of blood pressure because removal of both kidneys although profound azotemia is a consequence is not followed by the development of hypertension (Fig 26) Anastomosis between renal artery and renal vein although azotemia develops also does not result in hypertension It is well known also that acute nephrosis with uremia produced in animals

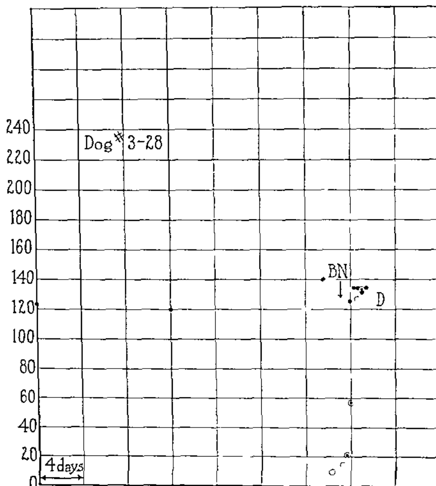


Fig 26 The effect of bilateral nephrectomy on the blood pressure Dog 3 28 male 16 6 Kg = Mean blood pressure mm Hg ○ = Blood urea nitrogen mg per 100 cc plasma BN = bilateral nephrectomy The blood pressure did not become elevated D = died The blood pressure did not become elevated despite the great azotemia which developed (After Goldblatt *Ann Int Med* 11 69 103 1937)

by various metallic poisons rarely results in any elevation of blood pressure. Also the shunting of the venous blood of a dog from the only kidney with renal artery constricted *through the liver by means* of a reversed Eck fistula neither prevents the development of hypertension after constriction of the main renal arteries nor lowers the blood pressure in hypertensive animals. This excludes any important *effect of the liver on the pressor substance of renal origin.*

The possible humoral mechanism of experimental renal hypertension was demonstrated more directly by the transplantation of a kidney to the neck or groin of a bilaterally nephrectomized dog or rabbit. When the renal artery of the transplanted kidney, with no nervous connection with the rest of the body, was constricted, a pressor effect resulted after the usual interval. The transplantation of a partially or completely ischemic kidney from one dog to the

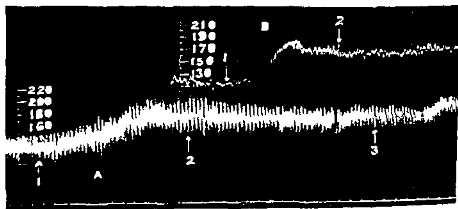


Fig. 27. Pressor action from the graft of an ischemic kidney. Blood pressure of two chloralosed, recently nephrectomized dogs in which an ischemic kidney from a hypertensive dog was grafted. A) At 1 the kidney from a hypertensive dog was grafted, at 2 *graft removed and anastomosed in dog B, at 3 graft reanastomosed.* B) At 1 the kidney which had functioned in dog A was grafted, at it was removed. Time in minutes. Blood pressure in mm. Hg. (After Houssay and Fasciolo, *J. t Soc. argent. de biol.* 13: 284, 1937.)

neck of a bilaterally nephrectomized dog resulted in an immediate temporary elevation of the blood pressure when the circulation to the ischemic kidney was restored (Fig. 27). This certainly indicated that some chemical substance from the ischemic kidney capable of bringing about peripheral vasoconstriction had been washed into the circulation. Whether or not this substance in the kidney is by itself

vasoconstrictor or whether it becomes vasoconstrictor after entering the blood stream is not elucidated by this experiment Another indication of the existence of a humoral mechanism was the demonstration that if the entire renal pedicle was clamped so as to occlude artery vein and ureter for from five to seven hours the sudden removal of the clamp was followed by a prompt elevation of the blood pressure When such a completely ischemic kidney was removed from the body without release of the clamp on the pedicle and it was then perfused with normal saline a powerful pressor substance was identified in the perfusate by the injection of the latter into the same or into another animal (Prinzmetal Lewis and Leo) It is now generally recognized that the chemical substances involved in all of the above experiments are probably identical Certainly the demonstration of a vasoconstrictor substance in the venous blood from an ischemic kidney (Figs 28 29) and of a vasopressor substance in the venous blood of an acutely ischemic kidney (Fig 30) and in the saline perfusate of a kidney of which the entire pedicle had been

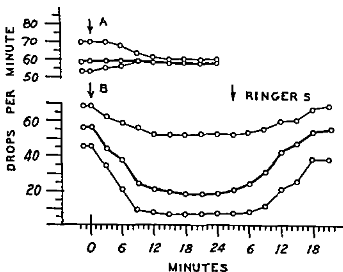


Fig 8 Vasoconstrictor action of renal venous blood on the vascular system of the toad *Bufo Arenarum* hensel according to the Lawen Trendelenburg method (A) Venous blood plasma from normal kidneys (B) Plasma from venous blood of ischemic kidneys of hypertensive dogs The fine lines represent the greatest and least vasoconstriction observed with each type of plasma The heavy lines represent the average action of the plasma from 15 dogs tested on 20 toads Note the constrictor action of the renal venous blood of hypertensive dogs (After Houssay and Taquini *Rev Soc argent de biol* 14 5 1938)

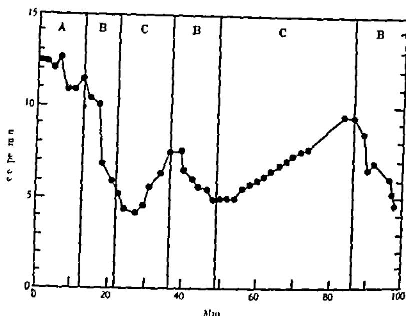


Fig. 29 Vasoconstrictor action of venous blood from an ischemic kidney Perfusion of the denervated leg of a dog with defibrinated blood (A) Blood from the heart lung circuit after functioning one hour (B) venous blood from ischemic kidney (C) venous blood from kidney with normal flow Note the marked vasoconstrictor action of the blood from the ischemic kidney (After Braun Menendez Fasciolo Leloir and Munoz *J Physiol* 98 83 1940)

clamped for several hours is positive evidence in favor of the humoral mechanism These investigations eliminated the probability that a nervous reflex from the kidney affecting the vasomotor apparatus plays a part in the origin of this type of hypertension and helped to eliminate the probability that the sympathetic nervous system plays a primary part in the origin of this type of hypertension

The presence of a vasoconstrictor substance in the blood plasma from the renal vein of a dog with experimental renal hypertension due to complete constriction of the main renal artery was demonstrated by some (Figs 28 29) by the Lawen Trendelenburg technique in the South American toad but not by others using other methods Some investigators failed to demonstrate pressor substances in the systemic blood of hypertensive dogs or of human beings and there was also no effect of blood from hypertensive dogs on the tonus of surviving arterial rings But Solandt and collaborators did observe a definite rise in the blood pressure of a bilaterally nephrectomized dog to which was given a direct tranfusion from a hyperten

sive dog and Braun Menendez and Fasciolo obtained a pressor effect in a normal dog as a result of the intravenous injection of 100 cc of renal venous blood from the transplanted renal ischemic kidney of another dog (Fig 30)

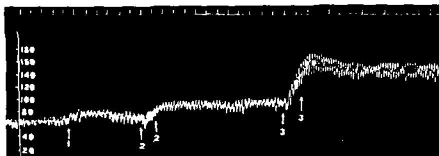


Fig 30 Pressor action of venous blood from an acutely ischemic kidney Injection of venous blood coming from a kidney incompletely ischemic for one hour Dog of 17 kgm chloralosed and nephrectomized Femoral blood pressure in mm Hg At (1) injection of 100 cc of normal saline into the jugular vein at (2) beginning and end of injection of 100 cc of jugular blood at (3) beginning and end of injection of 100 cc of renal venous blood Time in minutes Note the pressor action of the venous blood from the ischemic kidney (After Braun Menendez and Fasciolo *Rev Soc argent de biol 15* 161 1939)

It was soon shown that piperidomethyl benzodioxane (933F) did not have any greater effect on the blood pressure of a hypertensive animal than on that of a normal one whereas in both the effect of epinephrine was completely reversed by an injection of this substance (Fig 31) This indicated that the effective vasoconstrictor substance from the kidney was not sympathicomimetic

All of these investigations pointed to a chemical agent of renal origin as the probable cause of the elevated blood pressure The search for this hypothetical agent began with the repetition of some old observations made by Tigerstedt and Bergman which had been confirmed by some and denied by others and consisted of the demonstration of a substance in the crude saline extract of a normal rabbit kidney which was capable of inducing a pressor effect when it was injected intravenously into a normal rabbit To this substance they gave the name *Renin* and the English word *renin* has now been accepted for the basic principle of the humoral mechanism of experimental renal hypertension Prinzmetal and others found that there was a greater amount of this substance in the kidneys of dogs with experimental

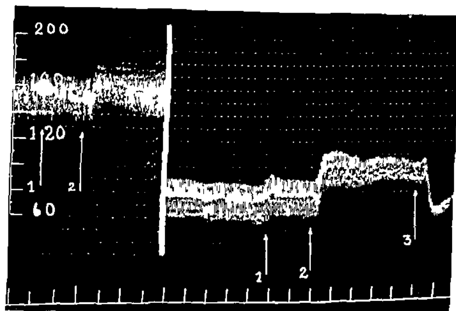


Fig. 31. Action of Fourneau 933 on the pressor action of venous blood from an acutely ischemic kidney. Twelve kgm. dog anesthetized with chloralose. Femoral blood pressure in mm. Hg. Time in minutes. (1) Injection of 15 cc. of control serum into the jugular vein. (2) fifteen cc. of serum from the renal vein of an ischemic kidney. (3) five gamma of adrenalin. At the break in the curves 0.01 gm. of Fourneau 933 per kgm. of body weight was injected. Note that Fourneau 933 does not alter the pressor action of venous blood from the ischemic kidney. (After Braun Menendez and Fasciolo, *Rev. Soc. argent. de biol.* 15:401, 1939.)

renal hypertension and of hypertensive human beings but not in rabbits. The stumbling block in the early experiments was the finding that this substance, which seemed to possess at least some of the basic requirements for the hypothetical pressor substance of experimental renal hypertension, still lacked any direct vasoconstrictor property, for it had no effect on the vascular system when it was dissolved in saline and perfused through a part (lower portion of a toad leg or tail of a dog) from which the blood had been washed out. Two independent groups of investigators (Braun Menendez and collaborators, Page and collaborators) discovered that renin is not directly pressor and that, although it is the key substance of the humoral mechanism, its effect is due to the reaction with a substrate in the blood and resultant formation of an entirely new substance which has vasoconstrictor and therefore pressor properties. To this substance the South American investigators gave the name Hypertensin

while Page and collaborators named it Angiotonin It was these earlier observations which led Landis in 1940 to write The evidence that renal ischemia raises the blood pressure by a humoral mechanism seems unassailable Yet even to this day some observers have concluded that there is no peripheral vasoconstrictor substance in the blood of hypertensive animals Because in a rabbit with blood pressure kept elevated by the constant infusion of renin the blood pressure did not fall as a result of pithing unless the infusion was stopped while it did fall when a hypertensive rabbit not receiving renin was pithed Dock concluded that in the latter the normal vasomotor mechanism was called into play and that vasoconstriction was therefore abolished It is at least possible that the immediate effect of the pithing was temporarily at least to abolish the output of the primary constituent of the humoral mechanism This should be investigated

Whether or not the normal kidneys play a part in the homeostatic regulation of normal blood pressure through the humoral mechanism of renal origin which begins with the entrance of renin into the renal venous blood is still not established although evidence is accumulating that it may play such a part It has been shown that in shock the secretion of renin is induced and it is thought that the low blood pressure which produces renal ischemia is the cause Although the existence of renin was discovered only about four years after the discovery of adrenalin by Oliver and Schafer and although the possible relationship of this substance to raised arterial pressure was obvious to the original investigators yet more than 40 years passed by before the existence of this substance was fully established One of the reasons for this was the failure of some investigators to corroborate the original findings of Tigerstedt and Bergman Notable among these investigations are those of Batty Shaw but because his results with extracts of kidneys and other organs were irregular and because he obtained pressor effects at one time and depressor at another he did not continue his investigations yet he concluded that a toxic agent leads to the liberation of sufficient renal parenchyma or if a sufficiently large district of renal tissue is cut off from the general circulation by obliterative vascular disease the cells involved may yield a pressor substance to the system and cause a rise of blood pressure above normal He should be given more credit for his contribution than has been done

in the past Other investigators who attacked this problem were really dealing with putrefactive pressor amines not with renin when they obtained pressor effects from the intravenous injection of autolyzed but not of fresh renal pressed juice

The stimulus for the renewed interest in renin came from the discovery of the method of producing persistent hypertension in animals by the constriction of the main renal artery In quick succession various investigators confirmed the existence of a substance like that of Tigerstedt and Bergman in crude and even in more purified extracts of kidney Tigerstedt and Bergman had shown how to separate the depressor from the pressor substance usually found in these extracts This was also confirmed It was also shown that the physiological effects on the circulation which result from the intravenous injection of renin are really not due to renin itself which is not vasoconstrictor but are due to the presence of hypertensin which is formed by the interaction of renin and a substrate in the blood plasma The physiological properties of renin are therefore those of the end product hypertensin or angiotonin as it has been named by Page and collaborators

The tendency at the present time is to accept the terminology suggested by the South Americans for the constituents of the humoral mechanism which is supposed to be as follows

Renin	an enzyme from the kidney enters the blood stream through the renal veins and acts upon	Hypertensinogen	a globulin in the blood plasma to form
Hypertensin	*a polypeptide which is the active vasoconstrictor substance and which can be inactivated by*	*Hypertensinase*	*an enzyme in the blood and in extracts of some organs*

Agreement upon this or any other single nomenclature would be highly desirable The one given above appears entirely acceptable

The following are brief summaries of the chemical and physiological properties of the substances which play a part in the humoral mechanism of renal hypertension

RENIN

Chemical properties Although renin has not yet been isolated in pure form yet all of its properties indicate that it is a protein or protein like substance or that it contains protein as a contaminant It is present in the press juice or in various extracts of renal cortex (not medulla) and does not occur in similar extracts of other organs It is unusually stable in solution and its physiological properties are not affected by lyophilization or freezing In solution in distilled water it deteriorates rapidly but if it is dissolved in 0.9% to 1.0% sodium chloride the stability of the protein is great In the liquid form heating to 55° C for 15 minutes does not destroy its activity but at 56° C and over it is rapidly destroyed It is resistant to the action of acid and is stable at pH as low as 3.7 and even lower but at pH 10 or over it is rapidly inactivated The addition of ammonium sulfate to a concentration of 1.4 to 2.6 molar precipitates renin from an aqueous solution at pH 6 It may also be precipitated with 0.38 to 0.41 saturated ammonium sulfate at pH 5 with saturated sodium chloride at pH 2 to 3 and with 0.7 to 1.0 saturation with magnesium sulfate In dilute solutions it is not precipitated by acidification alone at any pH Renin may also be precipitated from aqueous solution by the addition of 2 to 3 volumes of alcohol or acetone

The following reactions for renin have been summarized by Dexter It gives a positive biuret (peptide linkage) Millon (tyrosine phenols) Xanthoproteic (benzene ring) Hopkins Cole (tryptophane) Ehrlich diazo (histidine tyrosine) and Sakaguchi (arginine) Negative reactions were obtained with Molisch (carbohydrate) Sullivan (cystine cysteine) benzidine (pentose) Reactions for sulfhydryl groups were negative even after denaturation and treatment with cyanide By fusion with sodium however the presence of sulphur could be detected in the preparation The renin purified by Plentl and Page was shown to contain carboxypeptidases pepsinases trypsinases and amino peptidases Attempts at purification of renin by chromatographic adsorption by the use of a column of calcium carbonate and by adsorption on kaolin have been made Although Collings reported that passage through a Seitz filter resulted in a total

loss of the activity of renin yet we have been unable to confirm this and others have also succeeded in filtering renin through a Seitz filter without significant loss of activity Jonnard and Thompson found that renin in a crude extract migrated toward the cathode between pH 5 and 6 5 while the depressor substances migrated toward the anode between pH 5 and 7 5 In our own experience renin in relatively pure form migrates toward the anode at pH 7 6

Details of the preparation of renin have been given in original papers and in the book by Braun Menendez so they will not be given here The result of studies on the behavior of renin subjected to precipitation with ammonium sulfate and dialysis suggests that it is a pseudoglobulin but this has not been established Most investigators regard it as a proteolytic enzyme extractable by various methods from all mammalian kidneys and from the kidneys of other animals Winternitz and collaborators however have asserted that renin in very pure form is free of any enzymatic activity Most extracts with renin activity probably contain a mixture of enzymes and no specific single enzyme with all the characteristic properties of renin has been isolated Plentl and Page have excluded the action of amino peptidase and carboxypeptidase Various methods for the extraction and purification of renin have been described The preparation and isolation of renin by extraction is best carried out under aerobic conditions because anaerobic conditions favor the formation of putrefactive pressor amines tyramine isoamylamine and probably ethylamine An attempt to prepare it under sterile and anaerobic conditions has not been reported Kidneys from young rats have been reported to contain more renin than those from old rats but old rats are said to be more sensitive to parenterally administered renin These studies should be repeated on rats and other animals by use of more recently developed methods for the extraction and assay of renin

Physiological properties Renin is effective only when it is injected intravenously It is not vasoconstrictor when perfused through a circulatory system from which the blood has been washed out Most of the physiological properties including the pressor effect of renin are due indirectly to hypertensin which results from the interaction of renin and hypertensinogen a globulin in the blood plasma and which is the effective vasoconstrictor and true pressor substance The hemodynamic state of an animal after the intravenous injection

of renin is almost identical with that of an animal with experimental renal hypertension The site of action of renin itself is in the blood and not on the vasomotor endings of the peripheral arterioles or directly on the arteriolar muscle as was thought at first In the rabbit the pressor effect of renin is abolished or lowered by ether anesthesia but this is not true of the dog

An interesting phenomenon originally reported by Tigerstedt and Bergman and confirmed more recently by other investigators who used purer renin is *tachyphylaxis* This means a decrease of the response of an animal to repeated intravenous injections of the same amount of renin provided these injections are made only a few minutes apart before complete recovery from each injection has occurred (Fig 32) This effect is independent of anesthesia the type

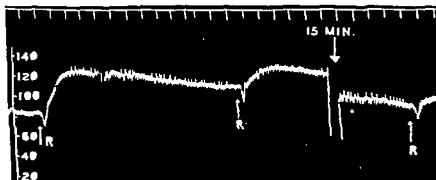


Fig 3 Tachyphylaxis to renin Effect of the intravenous injection of one cc of a solution of renin (R) on the blood pressure of a dog Note the diminished pressor effect in the second and third injection Time in minutes Blood pressure in mm Hg (After Braun Menendez E Fasciolo J C Leloir L F Munoz J M and Taquini A C (Translated by Lewis Dexter) *Renal Hypertension* Charles C Thomas Publisher Springfield 1946)

of anesthetic type or method of preparation of renin and occurs even in bilaterally nephrectomized animals This phenomenon is supposed to be due to a progressive decrease of the amount of hypertensinogen (Fig 33) but this has not been definitely established

Renin produces no direct effect on the isolated perfused heart The increased force of cardiac action which results from the intravenous injection of renin is directly attributable to the effect of hypertensin The effect of renin is not the result of the stimulation of an endocrine organ because it produces its effect in the absence of both

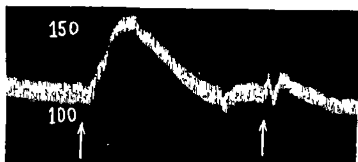


Fig 33 Disappearance of hypertensinogen from plasma by the injection of renin Hypertensinogen in the blood of a ten kgm dog before (first arrow) and after (second arrow) injection of 0 5 cc of renin per kgm ten cc samples of serum incubated ten minutes with an excess of renin Rise in blood pressure observed by injection of alcoholic extracts into a chloralosed dog Blood pressure in mm Hg (After Munoz Braun Menendez Fasciolo and Leloir *Am J M Sc* *200* 608 1940)

hypophysis and adrenals and acts even in an animal with spinal cord sectioned or destroyed It has been reported that in the rat renin acts when it is injected intraperitoneally and that it is more effective in the bilaterally nephrectomized than in the normal rat This phenomenon has not been reported for dogs or other animals Renin has a more prolonged vasopressor effect in bilaterally nephrectomized animals probably because of the increase of hypertensinogen in the blood of such animals The effect of renin in producing diuresis and increased excretion of sodium chloride is probably attributable to the hypertensin formed The intravenous injection of renin does not produce a reduction in peripheral blood flow or a fall in the temperature of the surface of the skin (Landis) Many of the studies which have been performed on the effect of various chemicals in inhibiting or enhancing the action of renin really deal with the effect of these drugs on the hypertensin which is formed as a result of the action of renin on hypertensinogen in the blood and will be discussed under the heading of hypertensin

In some of the earlier studies it was asserted that extracts of the kidneys of animals with experimental renal hypertension and of briefly and completely ischemic kidney contain more renin than the extract of the normal opposite kidney or of the normal kidneys from other animals Landis however was unable to correlate the renin content of the kidney and the physiological state of the kidney This work deserves more attention than it has received and should be

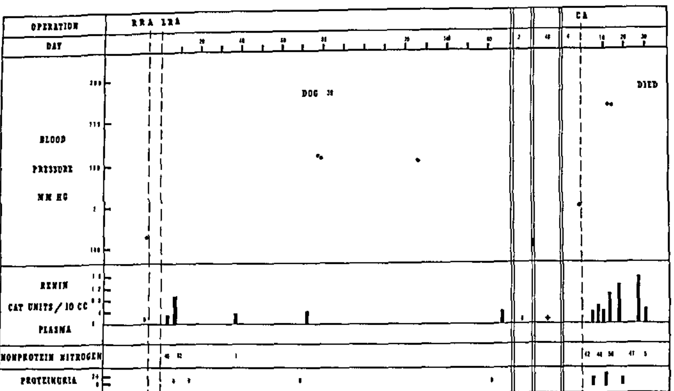


Fig. 11a. Effect of constriction of renal arteries on the concentration of renin in systemic venous blood of a dog. At RRA the right renal artery was constricted; at LRA, the left; at C.A., the capsular arteries were ligated. Note that if the blood pressure rises considerable amounts of renin were found in the plasma but that despite a persistence of the hypertension renin was no longer recoverable by the method employed. (After Dexter, L., Haynes, F. W., and Bridges, W. C., *J. Clin. Investigation* 24: 62, 1945.)

repeated now that the methods for extraction and assay have been perfected.

Renin itself has never been isolated from renal venous or systemic blood of animals with experimental renal hypertension. The presence of renin has always been inferred from the presumable demonstration *of hypertensin in the blood. In most of these studies hypertensinogen* was added to the blood samples and incubated with it to enhance the action of the small amount of renin present. By this method Dexter, Haynes and Bridges demonstrated the presence of renin in the systemic venous blood of dogs at least in the early phase of experimental renal hypertension. (See Fig. 33a.) By this indirect method Dexter and Haynes have also measured the amount of renin *in the systemic blood of human hypertensive patients.* They detected renin only when the blood pressure was rising abruptly (eclampsia and glomerulonephritis) and found none in the blood of patients with benign essential hypertension. For this reason they suggested that renin may be involved only in the beginning during the development of the hypertension. The presence of renin in detectable amounts in the renal venous blood from a human kidney of which the main *vein had been occluded for 12 minutes has been reported by* Dexter and Haynes. Most of the negative results that have been obtained have probably been due to the small quantity of blood tested. By the incubation of large quantities of blood with proper precautions to prevent the coincident action of hypertensinase we have been able to demonstrate the formation of hypertensin as a result of the interaction of the renin and hypertensinogen present in the blood of dogs with *experimental renal hypertension both benign and malignant.* In the malignant phase in animals there was much more hypertensin in the final product and therefore presumably more renin in the blood (Gollan, Richardson and Goldblatt).

The action of renin is not affected by hypophysectomy, thyroidectomy, splanchnicectomy, gonadectomy, splenectomy, pancreatectomy, abdominal evisceration or destruction of the spinal cord. Although bilateral adrenalectomy *has no immediate effect* yet it is followed by a progressive decrease in the response to the intravenous injection of renin.

It has been possible by slow intravenous administration of a small amount of renin *to keep the blood pressure elevated at least* 30 mm above normal for four hours (Hill and Pickering). Larger

quantities produced untoward circulatory disturbance. Hessel's assertion that repeated injections of renin lead to permanent hypertension has not been confirmed and Taggart and Drury failed to produce prolonged hypertension with the continuous injection of renin. The explanation for these differences is not clear but the subject is of sufficient importance to warrant more investigation.

The pressor response to an intravenous injection of renin is more delayed than the response to hypertensin because the beginning of the formation of the true vasoconstrictor substance hypertensin has to occur during this interval. It takes about 20 seconds after the injection is completed before a rise of blood pressure begins and the rise is not steep for it takes about two minutes for a unit of renin to produce its maximum rise of 30 mm Hg direct mean pressure. The return to normal is gradual and may take as long as 30 minutes (Fig 34).

It has been shown that the action of the purest renin so far produced is no different from that of crude renal extract provided it does not also contain a depressor substance. According to Grollman and collaborators the amount of renin in a kidney extract or its apparent concentration depends upon the care of the tissue prior to its preparation, the method of preparation, and the duration of time between the preparation of the extract and its assay on a test animal. The last statement must apply only to very crude and probably contaminated extract because a sample of our moderately purified sterile renin in solution in 0.9% saline kept at 4° C showed no significant deterioration during a period of 3 years.

Renin is not species specific for animals. All mammalian renin including human when injected intravenously produces a pressor effect in all animals but no renin except primate renin produces a pressor effect in man. A summary of the pharmacologic and hemodynamic effects of renin is given in Table 1.

Fate of renin in the body. The original idea of Tigerstedt and Bergman that the kidney eliminates renin has not been confirmed. It has been found that only when large quantities of renin are suddenly injected intravenously does it appear in small quantity in the urine. Under these conditions the maximum excretion occurs in about one hour after the injection. The absence of the liver and kidneys delays the rate of disappearance of renin injected intravenously. Because of this Leloir and his collaborators concluded that both organs play an

A summary of the pharmacologic effects of renin and the circulatory dynamics in hypertensive animals as published by Dexter in the book by Braun Menendez and collaborators (4) which is a modification of the summary published by Lewis and Goldblatt (1942)

TABLE I

Aspect Considered	Effect of Intravenous Injection of Renin Into Normal Animals	Experimental Renal Hypertension
Heart rate	No change	No change
Cardiac output	No change	No change
Total sympathectomy	Pressor action not reduced	Blood pressure not reduced
Destruction of cord	Pressor action not reduced	Hypertension not abolished
Hypophysectomy	Pressor action not reduced	Dampened but not completely prevented or cured
Thyroidectomy	Pressor action not reduced	Neither prevented nor cured
Gonadectomy	Pressor action not reduced	Neither prevented nor cured
Acute adrenalectomy	Pressor action not reduced	Rise of blood pressure produced by ischemic kidney grafts not prevented
Chronic adrenalectomy	Pressor action reduced or abolished Pressor action restored by desoxycorticosterone	Hypertension prevented or abolished Hypertension partially restored by desoxycorticosterone
Bilateral nephrectomy	Greater pressor effect	Greater rise of blood pressure produced by ischemic kidney grafts
Peripheral blood flow	Not reduced during rise of pressure	Not reduced in hypertensive rabbits
Renal circulation	Efferent glomerular arteriol constricted	Efferent glomerular arteriole constricted
Blood pressure		
a Fourneau 933	Pressor effect not inverted by Fourneau 933	F 933 produces same fall of blood pressure in normal and hypertensives
b Cocaine	Pressor effect not modified by cocaine	Cocaine produces no fall of blood pressure in dogs with hypertension from ligation of renal arteries
c Pulmonary artery pressure	No rise of pressure in pulmonary artery	Pulmonary artery pressure normal
d Duration of pressor action	Persistence of pressor action after a single injection no greater than 2 hours	Persistence of hypertension after removal of ischemic kidney usually greater than 6 hours
e Tachyphylaxis	Repeated injections produce tachyphylaxis	Persistent hypertension Normal or increased sensitivity to renin
f Permanent hypertension	Permanent hypertension has not been obtained by continuous injections of renin	Permanent hypertension

On the basis of differences observed between the effect of renin and of hypertensin on the blood vessels of the rabbit's ear (See page 79) Mylon and collaborators have concluded that the *in vivo* renin effect is not adequately explained by hypertensin formation This subject should be pursued

important part in the elimination of renin from the body It is now considered that the main mechanism of elimination of renin from the circulation is destruction by the tissues of the body including the kidney and liver In order that the results of all investigators might be directly comparable it would be well as soon as possible to decide upon standard units for the various constituents of the humoral mechanism and to establish standard methods of assay

Methods for the assay of renin The unit of renin In our work we have used direct intravenous injection of the test solution for the assay of renin and have defined the dog unit of renin as the quantity which when injected intravenously into a normal unanesthetized dog will cause a rise of direct mean pressure of 30 mm Hg *in at least three animals This has proved a very useful rapid* method for use in purification studies Leloir and collaborators on the contrary have defined a unit of renin as the quantity which when incubated with hypertensinogen in excess at 37 C and pH 7 5 produces 0 5 unit of hypertensin in 2 hours This is an indirect and slower method but is also satisfactory The advantage of the method is that minute amounts of renin can be detected in this way A comparison of the two methods has not yet been made A third procedure also suggested by Leloir and collaborators measures renin indirectly by the determination of the quantity of hypertensinogen which disappears from a solution containing a known amount This method has special use in the assay of human renin Full details are given in the book by Braun Menendez and collaborators (4) A method for the study of the reaction kinetics of renin has been described by Plentl and Page This also involves the determination of the amount of hypertensin formed and is also not a direct assay of the activity of renin



HYPERTENSINOGEN

Hypertensinogen is the substance with which renin reacts to produce the vasoconstrictor and therefore the true pressor substance hypertensin This constituent of the humoral mechanism has been demonstrated only in the blood plasma serum and lymph After the renewed interest in renin had occurred it was still thought for a while that renin was by itself a direct vasoconstrictor substance Although Kohlstedt Helmer and Page did find that impure renin possessed a moderate vasoconstrictor action on the isolated dog s tail yet they also showed that this action disappeared when the renin was purified by dialysis They also found that if the purified renin was mixed with plasma or heparinized blood the vasoconstrictor action *reappeared By the method of ultrafiltration of the plasma they* showed that the production of the vasoconstrictor action was a property of the colloid part of the plasma and not of the ultrafiltrate At first these authors considered that the vasoconstrictor action of renin was the result of its activation by a hypothetical enzyme *(a kinase)* contained in the plasma or whole blood and gave to this the name *renin activator* Braun Menendez and collaborators however in 1939 concluded that a new substance which they called hypertensin and which was vasoconstrictor resulted from the incubation of a mixture of renin with serum or plasma To the hypothetical substance in the serum with which the renin reacts they gave the name *hypertensinogen* and the vasoconstrictor substance they called *hypertensin* At about the same time Page and Helmer discovered the same substance to which they gave the name *angiotonin* It is now evident from all the work that has been done that it is the renin which acts upon the hypertensinogen to produce the hypertensin Page and collaborators have demonstrated that the substrate is present in the α-2 globulin fraction of the serum Because it is the substrate of renin and because this enzymatic reaction results in the formation of hypertensin the name *hypertensinogen* seems the most appropriate for it

Nature and properties It has now been shown that the hypertensinogen is a protein of the plasma thermolabile a pseudoglobulin and a constituent of the α 2 globulin fraction *not ultrafiltrable* and not

dialyzable. Hemoglobin, serum albumin, liver, spleen, thymus, testis, lung, heart, skeletal muscle or vegetable proteins do not act as renin substrate. Until now hypertensinogen has been found only in plasma, serum and lymph. It has not yet been isolated in the pure form. It is precipitated from the blood serum by ammonium sulphate between 0.30 and 0.41 saturation at pH 6.8 and does not precipitate after dialysis against distilled water. Heating at 60° C. for 15 minutes inactivates it, but it remains unchanged if kept at 50° C. for 1 hour. It is inactivated at pH 3.9 for 30 minutes at 37° C. but not at 25° C. Advantage is taken of this to obtain hypertensinogen free of hypertensinase which is inactivated at pH 3.9 and at 25° C. for 30 minutes.

Hypertensinogen from any mammal can serve as substrate for renin extracted from the kidneys of mammals and results in the formation of hypertensin. The only exception is man. Human renin, however, is active on the hypertensinogen of any mammal including man. Avian hypertensinogen does not act as a substrate for mammalian renin but forms hypertensin with avian renin. In proportion to the amount of substrate in the blood the amount of renin required for the reaction is very small and the amount of hypertensin formed is proportional to the amount of hypertensinogen. The reaction is hastened by incubation at 37° C. but it goes on to completion at much lower temperatures — even at 0° C. Other enzymes, such as pancreatin, papain and pepsin, or extracts of liver and spleen, do not have the same effect as renin on hypertensinogen.

Unit of hypertensinogen. The unit is best defined as the amount of substrate which, *with an excess of renin and in the absence of* hypertensinase, will produce one unit of hypertensin. The amount of hypertensinogen is considered proportional to the amount of hypertensin formed. In this reaction the presence of hypertensinase may result in faulty determinations. The latest technique suggested by Braun Menendez is [illegible] cc. of serum, plasma or globulin solution, 100 units of renin at pH 7.5 to 8 and between 37 and 40° C. for about 10 minutes. *To avoid the coincident action of hypertensinase, the best* procedure is to carry out the reaction at 0° C. for 2 hours (Sapirstein).

The quantity of hypertensinogen is about the same in the blood of normal dogs, cows and pigs, while the horse has a smaller amount (Leloir and collaborators). The amount contained in 1 cc. of plasma is approximately 0.75 unit in human, 0.45 unit in rat, and 0.35 unit

in dog plasma It has also been shown that lymph contains as much hypertensinogen as plasma In experimental renal hypertension and in benign human hypertension no increase of hypertensinogen in the blood has been demonstrated In some cases of human and experimental renal malignant hypertension with renal insufficiency an increase has been noted In the blood of bilaterally nephrectomized animals the amount of hypertensinogen is increased Hypophysectomy does not affect the hypertensinogen content of the blood It is greatly decreased in the blood of bilaterally adrenalectomized animals and in dogs with hemorrhagic shock If adequate substitution therapy is given to adrenalectomized animals the amount of hypertensinogen in the blood returns to the normal level Adrenalectomized animals have also been found to be less sensitive to an intravenous injection of renin In human hepatic insufficiency a decrease of hypertensinogen has been reported but no change was found in one case of Addison's disease (Dexter and Haynes) Repeated injections of renin reduce the hypertensinogen and in the tachyphylactic state the blood is said to be depleted of hypertensinogen (Fig 32)

It is highly probable that hypertensinogen is formed in the liver for it has been shown that the destruction of the liver by chloroform poisoning and also hepatectomy cause the hypertensinogen to decrease in amount and even to disappear from the blood It has been demonstrated that it is significantly decreased in human hepatic insufficiency but in a bilaterally nephrectomized and hepatectomized animal there is no diminution of hypertensinogen in the blood because no renin is being liberated to use up the substrate The same applies to shock in bilaterally nephrectomized animals

Preparation It has been found (Schales) that most of the hypertensinogen can be precipitated between 0 30 and 0 41 saturation with ammonium sulphate at pH 6 8 Saturated sodium chloride at pH 5 and 2M potassium phosphate have been used (Page) and Croxatto has advocated the addition of 3M potassium phosphate at pH 6 3 This precipitates both the hypertensinogen and the hypertensinase Further precipitation with 2M phosphate then precipitates the hypertensinogen and leaves the hypertensinase in the filtrate In this way relatively pure hypertensinogen is produced Full details are given in the book by Braun Menendez and collaborators (4)

HYPERTENSIN

The action of renin on hypertensinogen results in the formation of a new substance which is vasoconstrictor. This is the substance which causes the increased tonus of the smooth muscle of the arterioles and is therefore the substance which produces the pressor effect when renin is injected intravenously or presumably enters the blood stream from the kidneys of a hypertensive animal. To this substance Page and Helmer gave the name *angiotonin* and although they described some crystalline derivatives in the form of picrates and oxalates which they considered pure, yet as has been stated by Braun Menendez (4) until the melting point, elemental composition, relation between weight of the substance and pressor activity are determined, the isolation of this substance in pure form cannot be accepted. If hypertensin is finally isolated from the blood of hypertensive animals or man, the probability will become great that this is the substance that causes the persistently elevated blood pressure and then *hypertensin* will be the more appropriate term. It has been shown that when hypertensinogen is added to the plasma or serum of the blood of a totally ischemic human kidney and the two are incubated under conditions that prevent the destruction of hypertensin, a substance results which has all the properties of hypertensin. Despite some reports to the contrary, evidence is accumulating that renin and hypertensin are present in the systemic blood of hypertensive animals and man. This is one of the most important of the problems that still remain to be settled.

Chemical properties. As in the case of the other constituents of the humoral mechanism, the identification of hypertensin depends upon biologic methods because no specific chemical reaction for this substance has been demonstrated. Some of the chemical properties of this substance are now known. It is soluble in water, 96% ethanol, 75% acetone, liquid phenol, glacial acetic acid and methylene glycol, but it is insoluble in ethyl ether, chloroform and amyl alcohol. It is dialyzable and thermostable (resistant even to boiling temperature), alkali labile (destroyed completely by boiling for one hour at pH 10) and relatively acid stable, because it does not become inactivated by

boiling for two hours in 1N HCl Its purification has proved difficult It can be precipitated with phosphotungstic acid is destroyed by oxidation and acetylation with ketene but is not affected by reducing agents It is fluorescent and it gives the color reaction for arginine but it is not destroyed by the action of arginase Its only reaction for protein is a positive Sakaguchi It contains tyrosine and histidine but no cysteine tryptophane or proline By the method of electrophoresis it has been shown that hypertensin behaves as an amphoteric electrolyte of neutral character It differs from pitressin in being more resistant to boiling with acid produces a more rapid and shorter rise of blood pressure and does not induce tachyphylaxis *It differs from adrenalin in that its action is not inverted by 933F* or by ergotamine and it differs from tyramine in that cocaine does not appreciably alter its effect and also because hypertensin produces vasoconstriction in the toad while tyramine does not Its action is potentiated by veritol tyramine and ephetonine

That the reaction between renin and hypertensinogen is disintegrative is indicated by the fact that pepsin a known proteolytic enzyme may replace renin in this reaction but only at a very low range of pH But pepsin is inactive in the optimum range of pH for the activity of renin and does not produce a pressor effect when injected intravenously into an animal That the reaction between renin and hypertensinogen is enzymatic is not generally accepted *Hypertensin* is destroyed slowly by hydrolysis and by the action of proteases and peptidases It is now generally considered that hypertensin is a polypeptide of low molecular weight even though Page and Helmer found that it gave a negative biuret It is destroyed by pepsin trypsin papaine and extracts of some organs as well as by fresh normal blood plasma serum and laked blood corpuscles all of which contain an enzyme, hypertensinase which is capable of inactivating hypertensin The vasoconstrictor effect of hypertensin is inactivated by amino oxidase from liver of Sepia officinalis and by tyrosinase from Psalliota campestris (Crovatto) Cruz Coke lists a number of chemicals which partially or completely inactivate hypertensin the most *important* of them being iodine It is thought that the effect of the iodine is due to the transformation of the tyrosine in hypertensin He has also drawn attention to the accelerated destruction of hypertensin by hypertensinase when oxidized cytochrome C is added to a mixture of hypertensinogen and renal extract containing hypertensinase

Preparation and purification The optimum pH for the reaction between renin and its substrate is between 7 and 8 and the optimum temperature between 37 and 40 C The proteins are then precipitated by heat or by the addition of alcohol or acetone and the filtrate is concentrated by boiling or evaporation under reduced pressure Another method which has been described is the incubation of dialyzed renin and hypertensinogen recovery of the ultrafiltrate and concentration Sapirstein and collaborators have suggested incubation of renin and hypertensinogen at 0 C which practically eliminates the coincident action of any hypertensinase that may be present

Up to the present time all investigators who have tried to purify hypertensin have reported large loss of potency during the various steps During the process for unknown reasons it is often completely destroyed

The purification of hypertensin has been accomplished by Cruz Coke by means of anionic resin so that one unit had only 0 08 mg N Cationic resin adsorbed the hypertensin but it was not possible to elute it The melting point of this substance in pure form has not yet been reported Plentl and Page studied the effect of proteolytic enzyme on partially purified angiotonin but they concluded that such a study cannot be taken as offering proof of the structure of this substance

The most important recent contribution to the study of the purification of hypertensin is by Edman whose method consists of chromatography precipitation with nitranilic acid and electrodialysis In this way he obtained a 600 700 fold purification of the active principle but the yield was only 3 This great loss he attributed to the lability of the structure of hypertensin His highly purified hypertensin is almost forty times more effective in raising blood pressure than a comparable amount of tyramine phosphate As little as 0 5 gamma elicited an appreciable effect on the blood pressure of a cat He regarded his product as essentially pure judging by its behavior in partition chromatography on filter paper By means of electrophoresis he determined the isoelectric point to be pH 6 8 From the diffusion constant of this hypertensin in pure water he calculated the molecular weight to be 2700 By means of paper chromatography and some preliminary quantitative determinations he found in his hypertensin the amino acids lysine histidine glycine alanine serine proline valine tyrosine leucine (or isoleucine) as

partic acid and glutamic acid. Full details about methods of preparation and purification of renin are given in the appendix of the book by Braun Menendez (4).

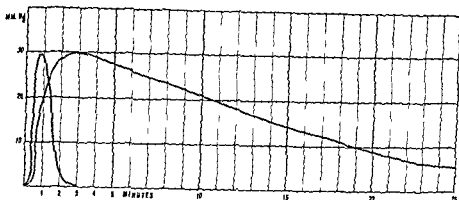


Fig 34 Diagrammatic representation and comparison of the effect of the intravenous injection of a unit of hypertensin and a unit of renin on the direct mean femoral blood pressure of an unanesthetized trained dog

Physiological properties The characteristic pressor effect produced by an intravenous injection of hypertensin is an almost immediate and steep rise like that of adrenalin (Fig 34). The maximum rise from a unit of hypertensin occurs usually in one minute or less and the return to normal in three minutes or less. As in the case of renin the hypertensive effect of hypertensin is not accompanied by a change in blood flow through the skin as measured by the temperature of the skin or by direct observation of the blood vessels growing in a wound of the skin of a rabbit's ear. The spleen and kidney show a decrease in volume and there is a decrease in coronary blood flow, increase of venous pressure and decrease of renal blood flow during the period of elevated blood pressure. Except for a forceful heart beat hypertensin produces no significant symptoms when it is injected intravenously into man. If the vagi are cut the dog's heart rate shows no modification as a result of the injection of hypertensin. The continuous intravenous injection of hypertensin produces an increase in blood pressure which is maintained during the entire period of injection (Fig 35). Hypertensin has a stimulating effect on practically all smooth muscle and this effect on intestinal strips has been used as a method for its identification and even its assay.

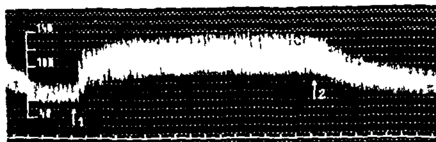


Fig 35 Continuous intravenous injection of hypertensin Dog 6 5 kgm chloralosed Double vagotomy Artificial respiration Femoral blood pressure in mm Hg Time in minutes (1) intravenous injection of hypertensin is started at a rate of one unit/min, (2) end of injection (After Braun Menendez Fasciolo Leloir and Munoz *J Physiol* *98* 83 1940)

In its pharmacological effects hypertensin is not specific It has shown its characteristic pressor effect in dogs chickens toads and snakes Toads and snakes but no other animals are rapidly rendered tachyphylactic by repeated injections of hypertensin Although Page and Helmer have reported tachyphylaxis to repeated injections of angiotonin by the method of perfusion of the rabbit s ear yet it is questionable that this method can be accepted for this demonstration The existence of an angiotonin activator also postulated by Page has not been confirmed The pressor effect of hypertensin is unaffected by intravenous injections of cocaine atropine ergotamine 933F or stilbesterol It is therefore not a sympathicommimetic substance An intravenous injection of hypertensin into a bilaterally nephrectomized animal gives an increased rise The intravenous injection of hypertensin produces a pronounced but transient rise in the potassium of the blood and a greater and more prolonged rise of sugar in the blood of dogs that are under the influence of chloralose No special significance has been attached to these observations and they have not been confirmed As has been said before the striking and significant difference between the pharmacological properties of renin and hypertensin is that hypertensin produces vasoconstriction when it is dissolved in Ringer s solution and perfused through an isolated organ from which the blood has been washed out while renin in Ringer s solution does not have this effect The direct effect of hypertensin and the indirect effect of renin are exerted on the musculature of the peripheral blood vessels A large dose of

hypertensin injected intravenously into normal persons causes a decrease in blood volume and cardiac output as measured by the ballistocardiograph. The effect of hypertensin injected intravenously is not altered by vagotomy, excision of the carotid bodies, splanchnic nerves, pituitary, pancreas, liver, adrenals, destruction of the adrenal medulla, rapid elimination of the central nervous system, or evisceration in cats and dogs.

Page and collaborators concluded that there is in the peripheral systemic blood of hypertensive animals and man a vasoconstrictor angiotonin-like substance not present in the blood of animals or man with normal blood pressure, but this finding has not yet been confirmed. There is also no proof that this hypothetical substance is identical with renin or hypertensin. Because these studies were carried out by the method of perfusion of the rabbit's ear, the result will require confirmation by some other method before it can be accepted. The same statement holds true for the demonstration of a pressor substance in blood that had been perfused through an isolated kidney with renal artery constricted, which was demonstrated by the same method.

Recently Gregory and collaborators failed to demonstrate an increase of vasoconstrictor substance in the ultrafiltrate of blood plasma of human beings with essential hypertension of long duration. They used the method of perfusion of the lower half of the frog for the demonstration of the vasoconstrictor substance. The method used is of questionable quantitative value. There is some doubt, therefore, that the results can be accepted unequivocally as proof that essential hypertension is not caused by an increased production of hypertensin or some other vasoconstrictor substance. Dexter and Haynes failed to demonstrate hypertensin when they added hypertensinogen and incubated it with the systemic blood of patients with essential hypertension. As a result of our own studies (Gollan, Richardson and Goldblatt — unpublished) the impression has been gained that the amount of blood tested hitherto has always been too small. Larger amounts of blood should be investigated. The failure of Grollman and Rule to demonstrate a pressor effect in the normal rat of parabiotic twins, of which one was hypertensive on a renal basis, does not disprove the existence of a humoral mechanism in this type of hypertension and does not prove the contention that the normal kidney elaborates a substance the absence of which results in hyper

tension. The explanation of their results may be simply the slow passage of the hypertensin from one animal to the other and the rapid destruction of that portion which does pass across.

Unit of Hypertensin. We have defined this as the quantity of hypertensin which when injected intravenously into the unanesthetized trained dog will give a rise of 30 mm. Hg direct mean femoral blood pressure in at least 3 dogs (Fig. 34). Braun Menendez and collaborators have published a curve of the pressor effects of various quantities of hypertensin from which the number of units is estimated by interpolation (Fig. 36). It would be highly desirable to agree upon a single method and a standard unit.

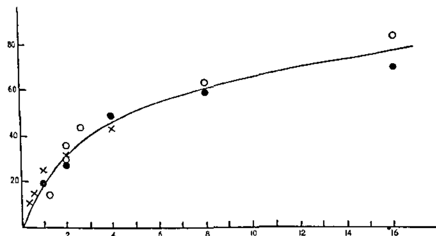


Fig. 36. Increase in blood pressure produced by different amounts of hypertensin. Abscissa: Units of hypertensin. Ordinates: Rise of blood pressure in mm. Hg. (After Braun Menendez, Fasciolo, Leloir and Munoz, *J. Physiol.* 98: 283, 1940.)

Recently Mylon and collaborators found that hypertensin is not vasoconstrictor for the rabbit's ear but that renin is. This is contrary to the results obtained by others using the Lawen-Trendelenburg technique in the giant toad. They also found that hypertensin which is not vasoconstrictive when perfused through the rabbit's ear becomes strongly vasoconstrictive if supplemented with traces of epinephrine or if fresh plasma is added. Of 20 amino acids tested for a similar property to that of hypertensin only tyrosine had it. The introduction of iodine into the tyrosine molecule entirely abolished the vasoconstrictor action. They concluded that constriction of the blood vessel of the rabbit's ear depends to a large degree upon traces of epinephrine and tyrosine-containing compounds of special configuration. This subject deserves more investigation.

HYPERTENSINASE

The observation by Page and Helmer that when renin is incubated with plasma or with serum angiotonin (hypertensin) is formed but that continued incubation results in the destruction of the angiotonin led them to believe that the continued action of the renin was responsible for the destruction of the angiotonin. Munõz and collaborators, however, showed that this inactivating effect of the renin could be eliminated while the capacity of the renin to produce the pressor substance remained unaffected. This led them to postulate the existence of another enzyme associated with impure renin to which they gave the name *hypertensinase*. Page and collaborators later conceded the existence of such an enzyme and to correspond with their nomenclature coined the name angiotonase for this enzyme.

Nature and properties. Hypertensinase is a hydrolyzing enzyme or group of enzymes with the ability to destroy hypertensin *in vitro* present in blood plasma and serum, in laked red blood corpuscles and in extracts of organs, especially intestine, kidney, pancreas, spleen and liver. Intestinal mucosa is the richest source of this enzyme, while blood serum and plasma that are not hemolyzed contain only a relatively small amount.

Hypertensinase is a protein, not dialyzable and precipitable by half saturation with ammonium sulfate. It is acid and heat labile and in neutral solution is quickly inactivated at 60° C. The optimum activity of hypertensinase is at pH between 7.5 and 8.5. It is inactivated if kept at pH 3.6 to 3.9 for 15 to 20 minutes at 37° C, even in the presence of renin and hypertensinogen. At 18° C the action of hypertensinase is greatly decreased and it becomes negligible at 0° C, at which temperature the reaction between renin and hypertensinogen is only slightly retarded and may go on to completion. It may be produced under anaerobic conditions (Fasciolo) and the optimum pH for the activity of hypertensinase not of renal origin is 7 to 8 (Munõz). For renal hypertensinase the optimum pH is 4 (Helmer), which indicates the probability that there are at least two enzymes of this type. Its activity is not affected by treatment with chloroform, thymol, toluol, octyl alcohol, potassium cyanide, sodium bisulphite, pyro

gallol and sodium fluoride The action of hypertensinase on hypertensin is regarded as monomolecular (Plentl and Page)

Pure hypertensinase has not yet been isolated but Croxatto and collaborators have concluded that its effect on hypertensin is due to a peptidase and most probably an aminopeptidase This is in agreement with the finding that the hypertensin inactivating effect of an extract of pancreas is due to carboxypeptidase They have concluded on the basis of inhibition experiments that the hypertensinase activity of renal extract and of laked red blood corpuscles is partly proteolytic and partly due to an oxidase effect It is difficult to obtain hypertensinase free of renin from renal extracts but in a solution of renin the hypertensinase may be easily destroyed by reduction of pH to 3 9

It is probable that the kidney may be the main source of the hypertensinase in normal blood plasma An indication of this is the almost complete absence of hypertensinase from the blood plasma of bilaterally nephrectomized dogs It has also been shown that there is less hypertensinase in lymph than in plasma The smaller amount of hypertensinase in the plasma of the blood from an ischemic kidney may mean simply that the ischemic kidney produces less of this enzyme What part if any hypertensinase plays in the maintenance of normal or elevated blood pressure has not yet been elucidated

The unit of hypertensinase We have used as the unit of hypertensinase the smallest amount which is capable of inactivating one unit of hypertensin in 30 minutes at 37 5 C For the assay variable amounts of hypertensinase are combined with a constant amount of solution known to contain one unit of hypertensin the mixture is incubated for 30 minutes at 37 to 38 C and is then injected intravenously into a normal unanesthetized trained dog The least amount of hypertensinase which destroys the entire unit of hypertensin so that there is no rise of blood pressure after the intravenous injection of the mixture is one unit of hypertensinase

Fasciolo and collaborators define the unit of hypertensinase as the amount which destroys 0 5 unit of hypertensin in 4 hours at 37 C and pH 7 4 in a volume of 10 cc with one unit of hypertensin originally present If exactly half a unit is not destroyed they calculate the amount by means of the graph in Fig 37

The amount of hypertensinase in the blood and in various

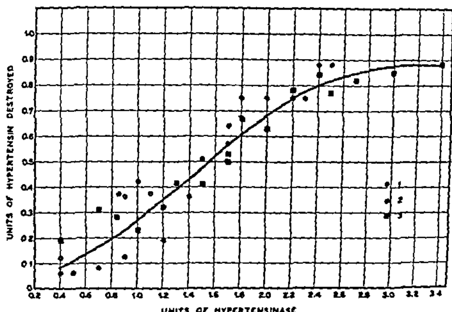


Fig. 37 Determination of hypertensinase Two hours of incubation at 37 C curve derived by Dexter for the calculation of units of hypertensinase one unit destroys 0.5 unit of hypertensin in four hours Dots circles and squares represent experiments on different days (After Dexter *Ann Int Med* 17 44 194)

organs In determinations of hypertensinase in plasma or serum account must be taken of the presence of hemolysis The hypertensinase content of red blood corpuscles is high and a small amount of hemolysis can greatly increase the quantity of it in the plasma or serum This accounts for some of the variable results that have been obtained Normal values for hypertensinase in the plasma of patients with hypertension or liver and kidney disease have been reported by Haynes and Dexter The observation of Weinstein and collaborators of a diminution of hypertensinase in the venous blood from an acutely ischemic kidney was not confirmed by Dexter and collaborators There is certainly no good reason for believing that variations in the concentration of hypertensinase in the plasma play a part in the course of experimental renal hypertension

The number of South American units of hypertensinase present in various organs of the dog are given in Table 2 Similar determinations on human tissues have not been reported

Mechanism of action of hypertensinase Hypertensinase is prob

TABLE 2 HYPERTENSINASE CONTENT OF DIFFERENT ORGANS OF THE DOG
Units per gram of fresh tissue

Intestinal mucosa	1200–1600
Kidney	800
Intestine	400 800
Pancreas	240
Spleen	160 200
Hemolyzed red blood cells	80– 120
Liver	80
Adrenal	40 50
Brain	4 8
Heart	4
Nonhemolyzed red blood cells	4
Plasma or serum	1 4

ably a hydrolytic enzyme contained in extracts of tissue and in blood There may be other enzymes in the body with the ability to destroy hypertensin Because hypertensinase activity is not inhibited in the absence of oxygen it is obviously not an oxidizing enzyme and because octyl alcohol inhibits amine oxidase but does not inhibit hypertensinase the identity of these two is also excluded Although tyrosinase can inactivate hypertensin yet it also inactivates tyramine and adrenalin Hypertensinase is not a phenol oxidase however because it is not affected by cyanide The possibility that hypertensinase is a carboxypeptidase has been excluded by differences from the latter in its action on various substrates As in the case of other constituents of the humoral mechanism so also all the work on the properties of hypertensinase will have to be repeated when it will have been isolated in pure form

MECHANISM AND SITE OF FORMATION AND RELEASE OF RENIN

The discussion of this topic was deferred purposely until the nature and properties of the various constituents of the humoral mechanism had been described

The determination of the exact mechanism and site of formation or release of renin is of great importance yet despite the vast amount of work that has been done on the properties of the various constituents of the humoral mechanism of experimental renal hypertension but little is known about this phase of the problem Although there are many like Leloir who consider that most of the known facts about the mechanism of action of renin are consistent with its being the basic cause of renal hypertension yet Grollman even now questions the existence of preformed renin in the kidney and considers that it is merely the product of autolysis *in vitro* This can certainly be disputed, for his experiments may merely indicate that in the renal tissue of the living animal there exists a renin precursor (prorenin) which is transformed into renin as it leaves the living cell and that the same transformation can also occur *in vitro* *Analogous phenomena are known to occur in the case of* other proteolytic enzymes of which trypsin is an excellent example

Exactly what takes place in the kidney with main renal artery constricted adequately to give hypertension which leads to the release or formation of renin is not well known The observation of decreased oxygen consumption by the ischemic kidney or by ischemic renal tissue has been confirmed but the significance of the result has been questioned on the ground that the reduction may have been due to the death of a certain number of cells and not to uniform interference with the *function of the cells*

The continuous inhalation of 100% oxygen for 48 hours failed to lower the blood pressure of hypertensive dogs and the inhalation of 7 to 10% CO did not cause a greater rise of the blood pressure in such dogs This has been interpreted as unfavorable to the view of a hypothetical anoxemic factor in the pathogenesis of experimental renal

hypertension Yet this is contrary to the view of Cruz Coke who has concluded that tissue anoxia especially renal plays an important part in the humoral mechanism of renal hypertension The demonstration of a great diminution of the cytochrome C concentration and of the activities of the cytochrome oxidase and succinic dehydrogenase in slices and homogenates of the kidneys of hypertensive dogs may be subject to the same criticism as the experiments on oxygen consumption Its *significance cannot be evaluated at the present time and more* work should certainly be done on this subject

The experiments on the origin of renin carried out *in vitro* have indicated that it originates in the cortex of the kidney and especially in the lining epithelium of the convoluted tubules The finding that the extract of an aglomerular marine fish kidney contains no renin proved of no great significance because it was shown later that marine fish kidneys which do possess glomeruli also do not contain renin while the kidneys of fresh water fish do possess it in considerable amount No explanation has been offered for this difference It is of interest in this connection that renin can be produced in the kidney of the dolphin which is a marine mammal The demonstration that the renin content of the involuting tubular portion of the mesonephros of the pig embryo decreases while that of the developing tubular portion of the metanephros increases and the failure to extract renin from kidneys in which the proximal tubules have been destroyed by sodium tartrate poisoning indicate that the convoluted tubules are most probably the site of origin (production and storage) of renin or at least of prorenin if this exists The exact nature of the stimulus for the release of renin or prorenin has not yet been determined The idea suggested by Page and collaborators that reduction of intra renal pulse pressure rather than decreased blood flow to the kidney is what determines the release of renin and the formation of the vasoconstrictor substance depends entirely upon the demonstration of a pressor substance in the blood by the rabbit s ear perfusion method This method is not accepted as a test for renin or angiotonin so it is questionable just what significance can be attached to these experiments Even the assumption of a presumable change from *intermittent to continuous pressure beyond the site of the afferent* glomerular arterioles is not justified for the very reason that a pulse pressure in the glomerulus has never been proved to exist Braun Mendenez goes so far as to state unequivocally that the idea that

diminished pulse pressure within the kidney causes the liberation of renin has no solid experimental proof The reduction of blood flow through the functioning components of the kidney (glomerular and peritubular capillaries) is another possible stimulus for the formation of release of these substances That there is a reduction in the blood flow through the kidneys in most persons with essential hypertension affecting both kidneys equally as well as in the early stages of renal hypertension is an established fact but there is still some question about whether permanent reduction in the blood flow is necessary for the persistence of the hypertension in animals The answer to this question must await better and more direct methods than are available at present for frequent determinations of renal blood flow before and after constriction of the renal artery Page and collaborators do not agree that some reduction of blood flow is a necessary condition for the development of hypertension merely because by indirect methods in an occasional animal they found no permanent reduction in the blood flow through the kidneys although there was still a slightly increased blood pressure For the demonstration of true renal ischemia Chasis and Redish require that the ratio of renal plasma flow (diodrast clearance) to tubular excretory mass (maximum tubular secretion of diodrast) should be calculated because the reduction of diodrast clearance does not necessarily mean renal ischemia Smith and co workers state that the evidence favors the view that the renal ischemia so frequently observed in essential human hypertension is a secondary event and that the primary event is the circulation of a humoral substance of unknown origin which brings about the efferent arteriolar spasm and progressive and parallel reduction in renal blood flow which they consider characteristic of essential hypertension Others believe that the efferent arteriolar spasm is due to the hypertensin produced by renin in the blood but in experimental renal hypertension this begins only after the renal artery is constricted therefore in man it should begin only when the renal arteries and afferent arterioles are sufficiently diseased to suffer a reduction in the size of the lumen

The demonstration *in vitro* by Doel of a normally perfusible vascular bed in the kidneys of human beings with benign hypertension especially when the perfusing fluid is kerosene certainly does not justify the conclusion that the perfusion of blood through the kidney *in vivo* is normal in such individuals It is interesting however that

despite the obvious objection to the method there was a great decrease in the rate of perfusion even of kerosene through the kidneys of patients with uremia due to arteriolosclerosis glomerulonephritis or pyelonephritis So little is known about the anatomy of the renal vascular bed and the effective circulation through the functioning components of the kidney that it is dangerous to draw any conclusions from experiments of this kind about the effect of intrarenal stenosing vascular disease or any other pathologic process capable of producing similar hemodynamic disturbance The existence of many intrarenal large arterio arterial and arterio venous anastomoses would nullify the significance of most perfusion experiments This phase of the problem is being investigated by Prinzmetal and collaborators who have demonstrated the existence of large intrarenal arterio venous communications but have not determined their number

In this connection the recent contribution of Trueta and collaborators (6) is of great significance Although they have not confirmed the existence of large intrarenal arteriovenous anastomoses in man or animal yet they have found that ischemia of the renal cortex partial or complete may be brought about by the by passing of the peripheral cortical circulation through the medullary and the juxta medullary cortical circulation which they have found adequate to carry the entire amount of renal blood so that venous return may be normal while peripheral cortical ischemia exists They have concluded that renal cortical ischemia may be induced even by intra renal cortical vasospasm of neurogenic origin As a result of these studies both direct and indirect determinations of venous return from the kidney become of questionable value as determinants of the effective supply of blood to the most important functioning components of the kidney which are situated in the cortex In the light of these findings also renal perfusion experiments have little or no significance The part that intermittent or persistent neurogenic renal cortical ischemia may play in the pathogenesis of human essential hypertension still remains to be established but the authors are committed to the view that this may be the common mechanism and that this type of hypertension may therefore be of renal origin

THE JUXTAGLOMERULAR APPARATUS

The problem of the possible part played by the juxtaglomerular apparatus in the *humoral mechanism of experimental renal and of* human hypertension is by no means settled This apparatus has been described in detail by Goormaghtigh and others

Goormaghtigh has reported an increase in the size of the juxtaglomerular apparatus *and in the number and size of the afibrillar* and sometimes granular or vacuolated cells of this apparatus in the kidneys of rabbits and dogs with renal hypertension (Fig 38) He has arrived at the conclusion that these cells may have a local or even general secretory or humoral activity and may therefore have a direct relationship to the hypertensive principle Afibrillar cells are common in the normal kidney of the rabbit but Goormaghtigh has found an increase in the number of afibrillar and granular cells in the juxtaglomerular apparatus of rabbits made hypertensive by the constriction

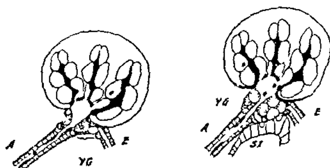


Fig 38 Juxtaglomerular apparatus and renal ischemia (A) afferent vessel (E) efferent vessel (YG) juxtaglomerular apparatus (SI) intercalated segment At the left, glomerulus from normal rabbit kidney at the right glomerulus of rabbit kidney after twenty one days of slight ischemia Hypertrophy of the juxtaglomerular apparatus and increase in the number of granular cells (After Goormaghtigh *Brit Med* 50 1541 1939)

of the main renal arteries He considers that the afibrillar cells have to do with the arteriolar tone and that *the granular cells are the source of* the pressor substance Dunihue has confirmed these findings and subscribes to the same views Kaufman has also reached a similar conclusion on the basis of an anatomical study of kidneys from normal

and hypertensive persons Graef and Smith however have drawn attention to the great variation in the appearance of the arteriolar media and the size and structure of the juxtaglomerular apparatus in normal man and animals and have cautioned that because of species differences for example the absence of granular cells in the kidney of man and dog the interpretation of the effects of ischemia must be contingent upon a more complete study of normal kidneys The development of cytologic changes in the juxtaglomerular apparatus interpreted by some investigators as indicative of endocrine activity does not constitute convincing proof of the origin of an endocrinogenic pressor substance or precursor in this structure

Up to the present time no direct convincing evidence has been offered that any special cells in the juxtaglomerular apparatus or preglomerular arterioles are the source of a chemical factor which constricts the afferent or efferent glomerular or peripheral systemic arterioles There is therefore no good reason for assuming that this apparatus is the regulator of glomerular blood flow or the indirect cause of the hypertension The very presence of renin in extracts of the kidneys of developing pig embryos in which a juxtaglomerular apparatus has not been identified militates against this view More investigation will be required before the functional significance of the juxtaglomerular apparatus and its relationship to hypertension can be properly assessed

THE TREATMENT OF HYPERTENSION

Medical Treatment

As soon as the production of experimental renal hypertension had been accomplished the most common methods for the medical treatment of human hypertension were also tried out on hypertensive animals, mainly the dog and the rat It had been found that in many patients with hypertension the intravenous administration of pentothal sodium caused a significant and sometimes a profound fall of blood pressure This is the type of patient who is usually chosen for treatment by surgical operation on the nervous system It was found also that in the excitable hypertensive or normal dog the blood pressure did fall moderately during the period of unconsciousness after the intravenous administration of between 10 and 15 mg of pentothal sodium per kilogram of body weight The same effect was noted as a result of the intravenous injection of pentobarbital sodium Such a fall indicated that in the excitable normal dog the pressure was probably high for a normal animal and that in the excitable hypertensive dog the hypertension which had developed after the constriction of the renal arteries was not entirely of renal origin and probably in part at least psychogenic In most of the normal and hypertensive quiet well trained animals no effect on the blood pressure was observed from the injection of the dose of pentothal or pentobarbital sodium mentioned or even after an injection of chloralosan

In our own experiments on the treatment of hypertension with any drug or method every animal was usually subjected at least once to an intravenous injection of pentothal sodium or of chloralosan If the blood pressure did not fall significantly during the state of unconsciousness the dog was regarded as satisfactory for the determination of the effect of other agents on the hypertension of renal origin A significant fall of blood pressure on the contrary was regarded as the indication that the elevation of the blood pressure was due in part at least to factors other than renal and the animal was not used for therapeutic tests Under these conditions morphine potassium thiocyanate mannitol hexanitrate viscum album (extract of mistletoe), allium sativum (garlic extract) extract of watermelon

seed sodium bromide veratrum viride acetylcholine choline chloride sodium chloride nicotinic acid and biotin proved ineffective Of the various substances that have a fleeting effect on human hypertension lowering the blood pressure by producing peripheral vasodilatation the nitrites are the most commonly employed In the dog with experimental renal hypertension as in man with so called essential hypertension the inhalation of amyl nitrite (pearl) or the intravenous injection of glycerol trinitrate (1/100th grain) lowered the blood pressure almost immediately In some animals the direct femoral mean blood pressure fell precipitously from a level well over 200 mm Hg to 30 mm or less The effect as in man lasted only a few minutes with a quick return to the original high level The administration of these substances at frequent intervals prolonged the effect by causing repeated falls of blood pressure but cessation of administration resulted in a prompt return of the blood pressure to the original high level

Of the various drugs that have been suggested recently for continuous or frequent administration in cases of human hypertension potassium thiocyanate is the best known For man it has been stated that if an adequate concentration of this drug in the blood is maintained by daily administration the blood pressure may in some cases be kept at a considerably reduced level and may even fall to normal In the dog with renal hypertension it has been found that the concentration of the drug in the blood must be at or very close to the level of intoxication before an appreciable fall of blood pressure occurs Intoxication indicated usually by anorexia vomiting and sometimes by diarrhea regularly preceded the fall of blood pressure to a lower level To obtain a concentration of 10 mg of this drug in 100 cc of blood the most effective concentration for man the dog required a relatively larger dose than is necessary for man Withdrawal of the drug resulted in a slow return of the blood pressure to the previously hypertensive level the rate of return depending upon the degree of intoxication of the animal In one of our animals it took a little more than two weeks for the return of the blood pressure to the original high level During the greater part of this time the animal was obviously ill Other investigators have also tested the effects of the injection of potassium thiocyanate in dogs with renal hypertension Davis and Barker found that it effectively lowered the blood pressure and that supradiaphragmatic removal of the thoracic

sympathetic trunks and splanchnic nerves rendered the animals even more sensitive to the drug Grollman Harrison and Williams found that potassium thiocyanate caused an insignificant fall when administered orally to hypertensive rats Hamilton and his associates found that sodium thiocyanate lowered the blood pressure of dogs with spontaneous hypertension but concluded that the season of the year (Summer) was more likely to have caused the reduction of the blood pressure than was the drug and the fall persisted for two months after all the thiocyanate was excreted Certainly on the basis of the experimental evidence there is no definite indication that potassium thiocyanate is a highly desirable drug for the treatment of renal hypertension Thus it would seem that all the methods which have previously failed to affect human hypertension are equally unsuccessful in experimental renal hypertension but that the difficulties involved in the clinical appreciation of the hypotensive properties of different agents in essential hypertension are greater than in experimental renal hypertension

Extracts of kidney A long time before persistent experimental renal hypertension had been produced in animals renal extracts of various types had been used empirically with variable results for the treatment of renal disease in man Organotherapy with renal substance extract or other type of preparation is not a new procedure for the treatment of human hypertension with or without accompanying disturbance of renal excretory function The thought that the kidney may be an organ of internal secretion dates back to 1893 when Brown Sequard assisted by d Arsonval was the first to prepare an extract of kidney for the treatment of this condition They treated the uremia associated with the anuria due to renal disease or to bilateral nephrectomy which they regarded as in part at least in the nature of hormone deficiency but they did not determine the effect of this treatment on the blood pressure Many other publications on the existence of an internal secretion of the kidney have appeared since then and treatment of nephritis and eclampsia with uremia by renal organotherapy has been the subject of many reports

Renal opotherapy for the treatment of hypertension with renal insufficiency was first practiced by Renaut in 1903 He used macerated kidneys and claimed that the daily administration of this material had a beneficial effect on both conditions

Actually the first organ to be extracted for the possible isolation of a substance that would lower blood pressure in man was the kidney Renal extracts specifically for the treatment of hypertension were first tried by Gomez in 1934 In 17 of his 40 cases of hypertension there was associated renal excretory insufficiency and accumulation of nitrogenous products in the blood He stated that there was a steady drop of blood pressure as the result of the treatment in 38 of his 40 cases and also a fall of blood urea in 16 out of the 17 cases in which there was elevated blood urea During the past few years there have been other publications dealing with the treatment of human hypertension by renal opotherapy and injections of renal extracts of various kinds

What prompted the trial of renal substance or extracts hitherto had always been either pure empiricism or the idea of the substitution of a missing or deficient renal hormone or the detoxification of the poisonous substances present in the blood because of disease of the kidneys The thought that such treatment might lower the blood pressure by inhibiting the formation of or destroying or neutralizing the effect of a pressor substance of renal origin or some substance in the blood plasma which interacts with the substance of renal origin to form a pressor substance is entirely new and is based on the current theory of a humoral mechanism of hypertension of renal origin

Any attempt to treat experimental renal hypertension by affecting the humoral mechanism should take into consideration the possibilities that have been outlined by Munõz and collaborators 1 suppression diminution or inactivation of renin 2 inhibition of the reaction between renin and hypertensinogen 3 diminution of the amount of hypertensinogen 4 inhibition of the action or destruction of hypertensin by an increase in the amount or activity of hypertensinase or of some other agent capable of accomplishing this

The first attempts to treat experimental renal hypertension by means of renal (and muscle) extracts were made by Harrison and collaborators who reported a lowering of the blood pressure in hypertensive rats by renal extract given by mouth or parenterally They assumed as the basis of their treatment that in temporary hypertension due to unilateral constriction of the main renal artery the normal kidney by some humoral mechanism for example by inhibiting or destroying the pressor substance might be playing a part in

eliminating the hypertensive effect of the kidney with the renal artery constricted There is other evidence for this view 1 The removal of a normal kidney in the presence of one with renal artery constricted causes the blood pressure to remain permanently elevated 2 *After removal of the ischemic kidney if the other is* normal the blood pressure falls to normal in 6 hours but it takes five times as long for the blood pressure to reach normal after the removal of both kidneys when one or both are ischemic It was this which led Katz and collaborators and others to the idea that by counteracting or neutralizing the pressor substance the normal kidney might play a part in the elimination of the chemical mediator of experimental renal hypertension They believe that the more rapid fall of the blood pressure to the normal level in the presence of normal kidney tissue as contrasted with the slow fall in its absence might be due to the excretion or destruction of the pressor substance by the remaining normal kidney They showed that in an animal with ureteral-venous fistula on the side of the normal kidney the removal of the opposite ischemic kidney was still followed by rapid (6 hours) fall of the blood pressure to normal They reached the conclusion that the normal renal tissue destroyed the pressor substance *since otherwise its continued presence in the blood* stream should have kept the blood pressure elevated for a longer period In the opinion of Dexter and Braun Menendez the renal threshold for the excretion of renin is too high to account for the possible stabilizing part played by the normal kidney Grollman and collaborators have adopted the view that the active principle derived from kidney tissue is an essential humoral agent the absence of which in the diseased kidney results in hypertension They now believe that the administration of this principle overcomes the deficiency and relieves the hypertension

The demonstration that renal vein blood from an ischemic kidney contains *much less hypertensinase than renal vein blood* from normal kidney would throw light on the earlier experiments of Freeman who found that normal dog s blood can reduce the blood pressure of dogs with experimental renal hypertension whereas blood from a hypertensive dog had no such effect The antipressor effect in this case may be due to the presence of hypertensinase in normal blood and its diminution in the blood of hypertensive animals However

this finding has not been confirmed More work should be done on this subject

The identical renal extracts used by Page and collaborators which caused a reduction of arterial blood pressure in their hypertensive animals and patients failed to have the same effect in the hands of some other investigators Although Page and collaborators have tried to relate the antipressor effect of their kidney extract to its hypertensinase content yet it has been shown that there is little hypertensinase in it and Schales and collaborators have found that this extract gave the same results when its hypertensinase was first completely destroyed There is certainly no proof that hypertensinase *per se* is absorbed into the blood stream from an intramuscular injection In fact it has been shown that for the antipressor effect of a renal extract for the treatment of hypertension hypertensinase is not required Harrison Grollman and Williams did not determine the existence of hypertensinase in their extracts but they reported a lowering of blood pressure in the rat dog and even man by the administration both orally and intramuscularly of a renal extract which contains no hypertensinase That such effects are caused by a renin inhibitor as postulated by Page and collaborators has not been confirmed

The possibility that all the effects on blood pressure by renal extracts hitherto reported are due to a non specific pyrogenic effect (with or without actual elevation of temperature) of a foreign organic material that produces a local and general reaction has already been suggested by several investigators It is interesting in this connection that a reduction in the severity of the local reaction as a result of purification of the extract also resulted in a corresponding reduction in the antipressor effect Schales Stead and Warren observed an antipressor effect which was not specific for renal extracts and attributed all the effects they observed to the local and general reactions which occurred In their opinion this invalidates any conclusions about the specific effect of any renal extract The same effect on blood pressure was obtained when the extract contained little or no hypertensinase if the local and systemic reactions to the injections occurred The extract which Grollman Harrison and Williams used can hardly be the same as that of other investigators because they found that the active substance was dialyzable and effec

tive by mouth in both animals and man. Most of their experimental work on animals was done on the rat and has not yet been confirmed. No other investigators have reported a lowering of the blood pressure in hypertensive individuals from the oral administration of renal extracts. Goldring and Chasis failed to observe a favorable effect in four hypertensive patients treated with renal extract by mouth even when they administered the equivalent of 50 kilograms of original kidney substance daily.

Although Page and collaborators insist that they have observed fall of blood pressure from renal extract without accompanying local or systemic reaction, yet it has been shown that all the effects can be produced by the parenteral injection of foreign organic substances such as milk and typhoid vaccine. There is certainly no clear indication that the renal extracts that have been prepared up to the present time constitute an adequate treatment for hypertension. Perhaps the fact that in the last 6 years there has been but little progress reported from the treatment of hypertension by these renal extracts is an indication of the difficulties involved.

Many different types of extract and other preparations of various organs, especially of liver and pancreas, have been prepared and administered empirically in a variety of ways for the treatment of human essential hypertension. The results for the most part have been equivocal and the claims for the value of these preparations by some have not been substantiated by others.

The results of the treatment of hypertensive animals by a great variety of substances that have also been administered to man are summarized in Table 5.

Antirenin. Treatment of hypertension by the parenteral injection of renin. Because renin is a protein, it was to be expected that it might be antigenic and that its parenteral injection would result in the development of an antibody in the blood plasma. What the properties of such an antiserum would be could not be anticipated, but it was hoped that it would at least prove to be antipressor, that is, antirenin.

Wakerlin and collaborators were the first to work on this subject and reported that in the blood serum of rabbits, dogs and guinea pigs, but not in the horse, injected with heterologous renin from various species, a substance or principle developed which was capable of neutralizing the acute pressor effect of an intravenous injection of

TABLE 3

Substance Employed	Animal	Daily Dose	Route of Administration	Period of Treatment Days	Effects on Blood Pressure
Nitrites and Nitrates					
Erythrol tetranitrate( )	Rat	0 03 gm	Oral	5	None
Erythrol tetranitrate( )	Rat	0 06 gm	Oral	5	Moderate fall
Erythroltetranitrate( )	Rat	0 0[illegible] gm	Oral	7	None
Mannitol hexanitrate( )	Dog	0 08 gm	Oral	1	None
Bismuth subnitrate( )	Rat	0 075 gm	Oral	8	None
Sodium nitrite( )	Rat	0 1 gm	Oral	5	None
Sodium nitrite( )	Rat	0 [illegible] gm	Oral	5	Moderate fall
Sulfocyanates					
Potassium sulfocyanate( )	Dog		I V		Fall
Potassium sulfocyanate( )	Rat	0 1 gm	Oral	5	None
Potassium sulfocyanate( )	Rat	0 [illegible] gm	Oral	5	Moderate fall
Potassium sulfocyanate( )	Rat	0 1 gm	Oral	7	None
Potassium sulfocyanate( )	Rat	0 [illegible] gm	Oral	7	Moderate fall
Potassium sulfocyanate( )	Dog				Moderate fall and toxic symptoms
Magnesium salts					
Magnesium carbonate( )	Rat	0 [illegible] gm	Oral	10	None
Magnesium sulfate ( )	Rat	0 05 gm	Oral	6	None
Choline salts					
Choline chloride( )	Dog	5 2 gm	Oral	[illegible]1	None
Acetylcholine( )	Dog	2 5 mgm	I V	44	None
Acetyl methyl choline hydrochloride	Rat	0 5 mgm	S C	5	None
Acetyl methyl choline hydrochloride	Rat	1 0 mgm	S C	5	Moderate fall
Bromides					
Sodium bromide	Dog	8 0 gm	Oral	10	None
Vegetable Extracts					
Allium sativum (garlic)( )	Dog	[illegible] 0 gm	Oral	60	None
Allium sativum (garlic)( )	Rat	1 0 gm	Oral	5	None
Allium sativum (garlic)( )	Rat	0 5 1 mgm	Oral	8	None
Allium sativum (garlic)( )	Dog	0 6 cc	Oral	15	None
Viscum album (mistletoe)( )	Dog	0 [illegible] gm	Oral	15	None
Veratrum viride (tincture)( )	Dog	1 cc	Oral	15	None
Watermelon seed ( )	Dog				None
Vitamins					
Vitamin A( )	Dog	200 000 to 400 000 U	Oral	90 180	Definite fall
Nicotinic acid( )	Dog	0 2 [illegible]0 gm	Oral	21	None
Biotin( )	Dog	1 000 U	S C	10	None
Vitamin B ( )	Dog	8 12 cc	Oral	4	None
Ascorbic acid( )	Dog	1 0 gm	Oral	1[illegible]0	None
Vitamin E( )	Dog	100 mgm	Oral	150	None

TABLE 5—*Continued*

Substance Employed	Animal	Daily Dose	Route of Administration	Period of Treatment Days	Effects on Blood Pressure
Tissue Extracts					
Pancreas (powdered)[ ]	Dog	0 3 gm	Oral	30	None
Pancreas (powdered)[ ]	Dog				None
Adrenal cortex[b]	Dog	0 1 cc /kgm	S C	30	None
Liver[ ]	Dog	6-12 cc	I V and I M	30	None
Pituitary[ ]	Dog	1 5 gm /kgm	I M	30	None
Hormones					
Estrone[ ]	Dog	0 1 mgm kgm	I M	30	None
Testosterone[ ]	Dog	2 5 mgm /kgm	I M	30	None
Pituitrin[ ]	Dog	10 U/kgm	I M	15	None

Each cc contained 0 15 mgm thiamin 0 01 mgm riboflavin 0 15 mgm pyridoxine 2 mgm nicotinic acid and 0 4 mgm pantothenic acid

1 Grollman, Harrison and Williams (1940a)
2 Friedman Jarman and Marrus (1942)
3 Goldblatt Kahn and Lewis (194)
4 Davis and Barker (1941)
5 Wakerlin and Gaines (1940)
6 Wakerlin Moss and Smith (194?)
7 Moss and Wakerlin (1944)
I V = intravenously
I M = intramuscularly
S C = subcutaneously

renin They found that if the antiserum was first mixed with the renin and kept for about 18 hours at about 4 C the mixture lost its pressor effect when injected intramuscularly into a normal dog Normal serum did not possess this property of inactivating renin They regarded this principle as analogous to an antibody an anti enzyme or antihormone and suggested for it the name *antirenin* This has been produced in the rabbit by the intramuscular injection of human hog cat and dog renin in the guinea pig by the intra abdominal injection of hog cat and dog renin and in normal and renal hypertensive dogs by the intramuscular injection of hog and rabbit renin The injection of homologous renin or of heterologous renin previously inactivated by heat did not induce the formation of antirenin in either normal or hypertensive dogs Hog liver extract failed to produce antirenin in normal or hypertensive dogs

Antirenin is a protein but it is neither an enzyme nor a precipitin In the dog and guinea pig even when the antirenin titer is high there is no precipitin in the blood In the rabbit in which precipitin re sponses are more easily obtained precipitins against other plasma pro teins are formed in high titer when these animals are given repeated intravenous injections of impure renin The fact that the rabbit serum

still retains its ability to neutralize renin after the precipitin has been removed by absorption *in vitro* certainly indicates that the antirenin and precipitin are not identical

In our laboratory in which the existence of antirenin was confirmed Dr Yale J Katz studied the chemical properties of this substance and found that it is precipitated quantitatively by ammonium sulphate at a concentration of 1 6 molar and pH 5 0 It is present in the pseudoglobulin fraction of the serum in which circulating antibodies are usually found and this fraction contains practically all the antirenin of the original serum Antirenin is active between pH 2 3 and 10 7 but is inactivated at pH 1 9 or less and 11 0 or more At 0 C and in the frozen or lyophilized state it remains stable for at least three months Heating of the antiserum at 65 C for ten minutes does not inactivate the antirenin but it is completely destroyed by heating at 75 C Antirenin does not neutralize the pressor effect of either hypertensin or pituitrin Like antihormones antirenin is not species specific in the neutralization of renin *in vitro* except for antirenin from rabbits induced by the injection of human renin This specificity is also true for antihormones produced in rabbits by the injection of extracts from other human tissues Hog antirenin produced in the dog will inactivate dog cow or hog renin but not human renin

Wakerlin and collaborators reported a fall of blood pressure to normal in dogs with repeated intramuscular injections of hog renin into hypertensive dogs They also observed the prevention of hypertension in dogs which received similar injections before the renal arteries were constricted Both of these observations we have been able to confirm (Goldblatt H Katz Y J and Richardson E) Wakerlin and collaborators found that the intraperitoneal injection of 40 ml of dog serum containing a high titer of antirenin for hog renin had no specific effect on the blood pressure of a hypertensive dog

No significant changes have been observed by Wakerlin or by us in those animals that developed high titers of antirenin in their plasma We have found that after a normal or hypertensive animal has developed a high titer of antirenin large doses of homologous or heterologous renin may be injected intravenously into them without producing any change in blood pressure We have injected intravenously in one dose as much as 100 dog units of hog renin without

noting any elevation of the blood pressure in a dog with ten units of antirenin per cc of its blood serum The kidneys of rabbits and dogs which had a high titer of antirenin in their blood were found to contain normal amounts of renin

Winternitz and collaborators failed to confirm the production of antirenin but they injected the renin intravenously Friedman and collaborators did not observe a fall in blood pressure in animals that received parenteral (not intravenous) injections of renin but they probably injected an insufficient amount of renin We too failed to detect the production of antirenin in dogs by the intravenous injection of as much as 25 units of hog renin a day for 12 weeks but by the subcutaneous and intramuscular injection of the same amount and even less we did succeed in producing antirenin of high titer in the serum of normal and hypertensive dogs We also observed a fall of blood pressure in hypertensive dogs and prevented the development of hypertension in dogs by repeated subcutaneous or intramuscular injections of hog renin before the renal arteries were constricted The optimum dose for this was 25 units of renin per day

Although Wakerlin and collaborators were the first to produce antirenin yet they now consider that they have good evidence that it is not the antirenin which is responsible for the prevention of hypertension or for the lowering of the blood pressure in dogs with renal hypertension The evidence upon which they have repudiated the significance of the antirenin is not conclusive One reason given is that highly purified hog renin is as effective as partially purified hog renin in stimulating the formation of antirenin but that it is much less effective as an antihypertensive agent It is highly probable however that this difference was due only to the smaller amount of renin injected Another reason was that in an occasional dog that received injections of hog renin which had been inactivated by heat a fall of blood pressure was also noted Not too much significance should be attached to this because in some untreated dogs the blood pressure also returns to a lower level and besides a non specific effect of injections of proteins associated with the impure renin can not be entirely excluded and may play a part in the phenomenon Wakerlin and collaborators also found no correlation between the antirenin titer and the antihypertensive effect This finding is contrary to the results of our own studies It is difficult to make a comparison between their results and ours because they did not give an

exact determination of the titer of antirenin attained by their animals and our methods of assay are not directly comparable Their antirenin titer has been based on the amount of renin extracted per gram of renal cortex which is obviously subject to considerable variation We have titrated the exact amount of antirenin by determining the number of units of renin inactivated by the serum Our dog unit of antirenin is the minimum quantity which neutralizes the acute pressor effect of our dog unit of renin

Possible application of the results obtained in animals to the treatment of human hypertension is beset with many difficulties Because homologous renin does not produce antirenin the injection of human renin into a hypertensive patient would probably be ineffective Whether heterologous animal renins which do not produce a pressor effect in man would nevertheless induce the formation of antirenin is still unknown Renin prepared from the kidneys of other primates which does produce an elevation of blood pressure in man would probably induce the development of antirenin in man but the difficulties involved in obtaining the large quantity of renin that would be required for this test are obvious Much work on this subject is still required It has not yet been given the attention it deserves

Other vasoconstrictor pressor and antipressor substances and their effects In any consideration of the humoral mechanism of renal hypertension mention should be made of the studies of Bing and collaborators which although they may have no direct bearing on this mechanism yet indicate a possible way whereby a pressor substance of renal origin may be formed or released under conditions which involve a disturbance of the intrarenal hemodynamics By perfusion experiments these authors demonstrated that an ischemic kidney but not a normal one is capable by decarboxylation of converting dihydroxyphenylalanine (dopa) a substance which possesses no pressor properties into hydroxytyramine which is a powerful pressor amine They showed that the amount of hydroxytyramine which is formed in the kidney from l dopa under conditions of oxygen lack is proportional to the reduction of blood flow through the perfused kidney and also demonstrated the transformation of dopa into hydroxytyramine in kidney extracts *in vitro* under conditions of low oxygen tension But even without the addition of l dopa the development of a pressor substance has been reported merely as a result of anaerobic conditions Liver spleen lung and heart muscle treated

in the same way did not develop pressor substances Liver and intestine also contain l dopa decarboxylase yet these organs were unable even when their circulation was reduced to produce hydroxytyramine from l dopa which was added to the blood

Bing was also able to show that partly or completely ischemic cat s kidneys *in vivo* converted l dopa injected intravenously into hydroxytyramine Oster and Soskin observed that the intravenous injection of l dopa into cats with experimental renal hypertension resulted in a great rise of blood pressure while no rise occurred in normal cats This is of great interest in this connection Bing and collaborators did not conclude that hydroxytyramine is the cause of or in any way directly involved in the pathogenesis of experimental renal or of human hypertension The same conclusion has been reached about tyramine As a result of his observations Bing merely concluded that the deamination of amino acids in the kidney may be catalyzed by amine oxidases and that this process requires oxygen In an ischemic kidney under relatively anoxemic conditions decarboxylation without deamination of amino acids would result in the formation of pressor amines an accumulation of which might result in elevated blood pressure It has been demonstrated that the two pressor substances hydroxytyramine and hypertensin are destroyed by different fractions of renal extract and by different mechanisms It has also been shown that renin does not effect the decarboxylation of l dopa to convert it to hydroxytyramine It has been demonstrated that the reduction of the blood flow to the kidney results in a profound alteration of the subsequent chemical events The kidney has the capability of converting the amino acid which is itself without pressor property into a powerful pressor amine which accumulates under anaerobic conditions and results in elevation of blood pressure Pressor amines are rapidly destroyed however by oxidative enzymes when the circulation is normal and aerobic conditions prevail Their work has provided a basis for the hypothesis that the hypertension which results from renal ischemia may be due to diminished deamination of certain amino acids and that it may possibly play an accessory or even an important primary part in hypertension in some types of animal

The work of Bing and collaborators has been the basis of the attempt made by others at the treatment of experimental renal hypertension in rats by means of quinones and in hypertensive dogs by

diketone 1-4 cyclohexandione Lowering of the blood pressure was reported but we have not been able to confirm any of these results by the use of the same materials in hypertensive dogs

Pressor amines certainly exist and produce their effects when injected intravenously into animals Deamination requires oxygen The question is whether some disturbance of the kidney may so reduce the available oxygen that deamination of natural amines does not occur and that the entrance of such amines into the blood stream results in hypertension There is as yet no available evidence from the studies on man that this mechanism plays a part in human hypertension The problem whether there is a renal mechanism of hypertension which is dependent upon a metabolic fault in the kidney which interferes with the utilization of melanin like substances and their phenolic precursors is not yet settled Even the possibility that such a mechanism exists in one animal the rat for example and not in other animals including man has not been determined with certainty

The studies on the treatment of human hypertension with amine oxidases have not led to an elucidation of this problem Schroeder and collaborators found that the parenteral injection of tyrosinase a phenolic oxidase capable of oxidizing both mono dihydro oxyphenols and ortho hydro oxyphenols to inactive quinones reduced the blood pressure in rats and dogs with experimental renal hypertension and in man with essential hypertension He showed also that tyrosinase can inactivate renin *in vitro* in the presence of catechol But Prinzmetal and collaborators showed that the effect obtained by Schroeder was probably due to the local and systemic reaction induced by this material and not to the enzymatic activity of the tyrosinase because an extract containing it was also effective when the tyrosinase activity was first destroyed Alles Blohm and Saunders concluded that the amount of tyrosinase injected by Schroeder was much less than would be required for the oxidation of diphenolic amines This subject deserves more investigation

Croxatto and collaborators have shown that pepsin if it acts on blood globulin at pH 3 0 or lower can produce by peptic digestion of the protein a vasoconstrictor and pressor substance which they have called *pepsitensin* and which they assert is identical in chemical and pharmacological properties with hypertensin except that pepsitensin is not inactivated as rapidly by hypertensinase from red blood

corpuscles This difference they attributed to impurities in pepsitensin and asserted that the purer the pepsitensin the more sensitive it is to inactivation by hypertensinase and other proteolytic enzymes It has been found also that hypertensin is more easily destroyed than pepsitensin by the action of pepsin This is to be expected since pepsitensin results from the action of pepsin on blood globulin The reaction is usually carried out with the hypertensinogen at pH 3 5 but a pH of 5 to 6 for 30 minutes is considered best (Weber Major and Lobb) and it will occur when the pH is up to 7 but not higher In this respect the action of pepsin differs from that of renin Depressor substances may also result These have caused difficulties in attempts at purification and may even mask the pressor effect According to Alonso an effect similar to that of pepsin may result from prolonged treatment with acid Renin and pepsin also do not act upon exactly the same substrates Plasma globulins acidified to pH 2 4 for 30 minutes at 25 C and then neutralized or precipitated with alcohol and redissolved no longer yield hypertensin with renin but still yield pepsitensin with pepsin It would seem therefore that pepsin acting on denatured globulin is capable of producing a pressor substance while renin fails to do so It is of interest that hypertensinogen after treatment with renin cannot react with pepsin to form pepsitensin The existence of pepsitensin has been confirmed by others including ourselves Helmer and Page have produced it with crystalline pepsin Croxatto has obtained pressor substances from the action of pepsin on other substrates such as casein ovalbumin lactalbumin and lactoglobulin but not gelatin Renin does not act upon these to form hypertensin Trypsin pepsin and taka diastase do not have the pressor substance producing properties of pepsin

Just what significance all of these experiments will have in connection with the humoral mechanism of renal hypertension it is still difficult to estimate For the present these observations merely indicate the probable non specific character of the renin hypertensinogen reaction and the disintegrative enzymatic nature of this reaction which results in the formation of an active pressor substance

The observation that both hypertensin and pepsitensin are inactivated by an amino peptidase obtained from yeast has led Croxatto to conclude that the hypertensinase activity of renal extract may also be attributed to the enzyme amino peptidase contained in renal tissue

They have also shown that the vasoconstrictor effect of hypertensin tested on the perfused toad is destroyed enzymatically by the action of amine oxidase and tyrosinase In our own laboratory in collaboration with Gollan and Richardson much work has been done on enzymes from many plants that are capable of inactivating hypertensin *in vitro* It is difficult to make preparations that are not toxic and although antipressor effects have been obtained in hypertensive dogs yet it is difficult to estimate how much of the effect was due specifically to the plant hypertensinase

Shorr Zweifach and Furchgott in their studies of the humoral mechanism of shock have obtained results which may prove in part at least applicable to the humoral mechanism of renal hypertension From the kidney they have obtained a vaso excitor material (VEM) which has the ability when injected intravenously of potentiating the vasoconstrictor effect of the topical application of adrenalin on the terminal arterioles and precapillaries of the mesoappendix of the rat VEM is not itself a direct vasoconstrictor substance and it has not yet been isolated in pure form They have found that VEM is also present in blood plasma in the irreversible phase of shock and in experimental renal hypertension due to constriction of the main renal arteries From slices of normal kidney VEM is obtained only under anaeorbic conditions but from the ischemic kidney of the hypertensive animal the extract may be obtained under aerobic conditions as well The aerobic production of VEM from the kidneys of hypertensive dogs is believed to be due to the loss of a renal mechanism for the inactivation of VEM

From liver and skeletal muscle these authors have also isolated a vasodepressor materal (VDM) which has the ability to inhibit the vasoconstrictor effect of the topical application of adrenalin Vaso inhibitor material (VIM) would have been a more appropriate name for this substance VDM is not itself a direct vasodilator and it has not yet been isolated in pure form From normal liver the VDM is extractable only under anaerobic conditions From the liver a substance has also been obtained which is capable of destroying VDM under aerobic conditions Extracts prepared from livers removed during irreversible shock or previously subjected to anaerobic incubation for two hours failed to inactivate VDM They have called this substance VDM oxidase which is said to consist of two components a heat labile apoenzyme and a heat stable coenzyme Neither

one of these has been isolated in pure form Their exact nature has not yet been determined

There is but little doubt that none of these substances is identical with any of the known components of the humoral mechanism of experimental renal hypertension yet they may play an important part in either potentiating or neutralizing the vasomotor effects of some of these substances The possible part they may play in the maintenance of normal blood pressure and the possible contribution to our knowledge of the pathogenesis and therapy of hypertension which may result from these studies cannot yet be determined from what has been published This work is of the greatest interest and importance and should be pursued by these authors as well as by other investigators

The most recent contribution to the subject of the humoral mechanism of hypertension has been made by Shipley Helmer and Kohlstaedt and has been published only in preliminary form These authors have discovered a pressor principle in the blood plasma of cats dead as the result of certain undiagnosed natural causes of DDT poisoning or of prolonged hypotension resulting from large withdrawal of blood The intravenous injection of plasma from such animals caused a sustained elevation of blood pressure for as long as five hours in cats which had been bilaterally nephrectomized two days before but not in normal cats This effect occurred with or without anesthesia even in the pithed nephrectomized test animal This pressor principle appears to be distinct from renin angiotonin pepsitensin hydroxytyramine or tyramine because of the difference in the contour and duration of the pressor response and the difference in the conditions under which the response is observed The authors failed to find this principle in the blood plasma of bilaterally nephrectomized cats which had been poisoned with DDT or in which prolonged hypotension had been produced by excessive bleeding or in animals azotemic as a result of bilateral nephrectomy They also failed to find it in the blood plasma of normal living cats or of normal cats which had been killed suddenly by various means They concluded that a moderately prolonged period of hypotension (with concomitant diminished blood flow and/or blood pressure within the kidneys) is necessary for the production of this pressor principle They have not yet isolated this substance in pure form but have con

cluded that it appears to be protein in nature is heat labile and does not pass through a dialyzing membrane or ultra filter The active substance is partly but not completely precipitated at pH 4 by saturation with sodium chloride or 0 6 saturation with ammonium sulfate Although it has been demonstrated that renin does appear in the blood in the state of hypotension due to excessive bleeding yet the amount of renin present is not sufficient to account for the pronounced and sustained pressor reaction of the plasma which would come from the hypertensin produced by the renin in the amount of plasma used in the experiments mentioned above The injection of a fresh solution of renin extracted from cat kidneys possessing the ability to produce hypertensin *in vitro* did not cause the same marked or sustained pressor response in the pithed bilaterally nephrectomized cat Of great interest is the fact recently reported by the authors (Second Conference on Factors Regulating Blood Pressure sponsored by the Josiah Macy Junior Foundation New York) that this new sustained pressor substance (SPS) is also inactivated by antirenin produced with impure renin

The fact that this new pressor substance produces such a sustained effect is of great interest There does not appear to be any obvious connection between this pressor substance and the substances described by Shorr and collaborators The significance of this contribution to the problem of the humoral mechanism of renal hypertension and the regulation of normal blood pressure remains to be determined

On the basis of experiments on renal hypertension in the rabbit Pickering has concluded that only the initial phase of this type of hypertension is due to the renin hypertensin mechanism and that the persistence of the hypertension is due not to a neurogenic mechanism as proposed by Ogden but to another humoral mechanism Because the pressor substance involved in the latter is not of renal origin it is not identical with that of Shipley and collaborators Much more work is required before the exact nature of the mechanism involved in the acute and chronic phases of experimental renal hypertension can be considered as established

The effect of diet on experimental renal hypertension has not been exhaustively investigated It has been asserted that a high protein (800 grams of meat daily) diet or 50 grams of urea daily increases

the elevated blood pressure in dogs with experimental renal hypertension A diet that produces a considerable gain of weight has a similar effect

The significance of the experiments of Calder on the production of hypertension in the rat by a diet deficient in the heat stable fraction of the *vitamin B complex* is of interest His belief is that the hypertension is of metabolic origin and due to diminished oxidative processes in the kidney In this way he relates his results to those obtained by constriction of the main renal arteries This work requires confirmation

The claim for the effectiveness of *ascorbic acid* in reducing hypertension in man has not been confirmed This has not been tested on hypertensive animals It has been reported that *vitamin F* has no effect on the blood pressure of dogs with experimental renal hypertension This has not been tested on hypertension in man

The assertion that large doses of *vitamin A* lower the blood pressure of hypertensive human beings rats and dogs has not been substantiated by the same investigators (Wakerlin and collaborators) who finally decided that it was not the vitamin A that produced the effect because fish body and liver oil still contained the blood pressure reducing substance when the vitamin A was destroyed In fact Grollman and collaborators found that a highly purified vitamin A concentrate did not have the hypotensive effect and that the effect was enhanced by the oxidation of the fatty acids in the effective marine oil The nature and mechanism of the action of this substance in marine oils are not known In his most recent publication on this subject Grollman asserts that a number of refined oils derived from marine fishes and from the seeds of the tung tree administered orally reduce blood pressure in hypertensive rats dogs and man Vegetable oils were not effective in hypertensive animals Oxidation and saponification prior to oxidation enhanced the activity of some of the active oils The effect was independent of their original vitamin A content and was retained after the destruction of this vitamin The active principle is soluble in water and dialyzable as in the case of the orally effective renal extracts with which he is now inclined to consider this material identical He states however that it is still impractical to treat patients because there is no readily available source of large amounts of this principle

It has been reported that vitamin A may affect urea and inulin

clearances but these authors did not control their experiments by giving the same product with the vitamin A inactivated *Vitamin D_2* given by mouth has no effect on the blood pressure of the hypertensive rat (Briskin) Another sterol that has no effect on experimental renal hypertension of the dog is *testosterone* (Wakerlin and Gaines)

As a result of experiments in which they noted a disequilibrium of sodium balance in hypertensive rats Grollman and collaborators tested the effect of restriction of sodium intake on hypertension in the rat and in man They noted a lowering of blood pressure in both The significance of these observations especially with relation to the part played by the cortex of the adrenal remains to be elucidated

Kempner has reported the blood pressure lowering effect of a diet consisting mainly of rice and other observers have confirmed this effect in at least some cases The outstanding characteristics of this diet are the low protein and low sodium content Whether the effects that have been observed are attributable to the low sodium the low protein or both has not yet been established There are those who believe that the effect is due mainly if not entirely to the low sodium content of the diet Some observers have failed to observe any significant lowering of blood pressure as a result of this diet Recently Dick reported a fall of blood pressure in dogs with chronic experimental renal hypertension that had been fed the rice diet

According to Kesson and McCutcheon there is no relationship between the level of blood pressure and retention of calcium in man This relationship has not been investigated in animals

Surgical Treatment of Hypertension

The various surgical procedures that have been carried out on the nervous system for the treatment of human hypertension have all failed to affect experimental renal hypertension Even total sympathectomy of the abdomen and thorax including denervation of the heart and destruction of the spinal cord have had no permanent effect on experimental renal hypertension in the dog (Freeman and Page) (Fig 22) The disturbance of renal hemodynamics produced by the clamp cannot be altered by these procedures but the effect on the vasomotor mechanism should be the same as in man It is at least pos

sible that the reduction of the blood pressure which has been recorded in human beings as the result of surgical interference with the nervous system may be due in some way, and in part at least to the resultant improvement of the circulation in the kidney There is no proof however, that this improvement does occur If the lowering of the blood pressure in man is not due to improvement of the renal circulation then it must be admitted that in the dog the effect on the vasomotor apparatus of various surgical procedures on the nervous system are for reasons unknown not as effective as in man This difference may have to do with the usual orthostatic position of man as compared with the natural horizontal position of quadrupeds It is well known that especially in the early stages after sympathectomy in man the blood pressure falls only or to a greater extent when the erect position is assumed and that it frequently returns to the original high level when the patient is in the horizontal position The experiments on the animals do not in any way controvert the results that have been obtained so far by sympathectomy in the treatment of hypertension in man It is possible that in some cases of human essential hypertension stimuli from the central nervous system play a part even if only a secondary one in elevating the blood pressure It may be that this is the factor that is most commonly influenced by the usual medical or surgical treatment of essential hypertension and accounts for most of the fall of blood pressure that is produced by such treatments

Unilateral nephrectomy for hypertension due to unilateral renal disease Reference has already been made to the production of experimental renal hypertension in animals by constriction of the main artery of only one kidney and to the cure of the hypertension by the release or removal of the clamp on the renal artery or excision of the kidney with renal artery clamped at a time when the blood pressure is still considerably elevated The resultant recognition of the existence of human hypertension associated with unilateral renal disease especially unilateral chronic pyelonephritis and the usual accompanying renal vascular disease or any other pathologic condition capable of producing the same alteration of intrarenal hemodynamics and the cure of the hypertension in some cases by excision of the diseased kidney has also been mentioned In man the first type of unilateral renal disease that was incriminated was chronic pyelonephritis and Butler was the first to show that the removal

of such a diseased kidney resulted in the prompt return of the blood pressure to normal Since then other investigators have removed a pyelonephritic kidney, when the other kidney was considered normal and, in some instances the blood pressure returned to normal and has remained normal for as long as 6 years In man as in some dogs and frequently in goats sheep and rats the hypertension evidently may persist for a long time on the basis of unilateral renal disease In those cases in which the blood pressure failed to return to normal it may be assumed either that the remaining kidney was also diseased but that the disease was not recognizable on account of the absence of renal excretory impairment or that the residual hypertension was not of renal origin In recent years there have appeared reports of cases in which hypertension was found associated with unilateral renal disease of other types and in which removal of the diseased kidney also resulted in the return of the blood pressure to normal Congenital abnormality with stenosis of one renal artery arteriosclerotic narrowing of the orifice of one main renal artery caused by arteriosclerosis of the aorta itself or of the first part of the renal artery arteriosclerotic stenosis in any portion of the main renal artery thrombosis of the aorta at the mouth of the renal artery or in the main renal artery aneurysm dissecting or otherwise of the aorta with compression of the main renal artery unilateral renal panvasculitis and extrinsic tumor pressing on a main renal artery are all illustrations of the types of unilateral renal disease associated with hypertension that have now been observed in man The return of the blood pressure to normal as a result of the removal of such a diseased kidney has already been reported in cases of human hypertension in which one kidney was diseased and the other obviously normal or not significantly affected The subject has been reviewed in great detail by Abeshouse who has given a complete bibliography of the published work on this subject In personal communications to the author there have now been mentioned more than 50 unpublished cases in which nephrectomy for unilateral renal disease has resulted in a return of the blood pressure to normal for periods varying from 3 months to 6 years In most of these cases the disease was unilateral chronic pyelonephritis with the usual intrarenal stenosing vascular disease that accompanies this condition In man when the presence of disease in one kidney is established it is often difficult to determine with certainty whether the other kidney is affected and especially

whether it is the seat of arterial or arteriolar sclerosis All studies of the presumably normal kidney including clearance tests of various kinds for renal excretory function may give results that are within the limits of normal nevertheless this kidney may be the seat of considerable vascular disease It is impossible therefore to predict with certainty in human beings the probable effect on the hyper tension of the removal of one obviously diseased kidney If the other kidney is actually normal the probability is great in the light of the experimental studies on animals and the results already obtained from unilateral nephrectomy in man that the blood pressure will return to normal and remain at that level after the removal of the diseased kidney If the other kidney is known to be diseased or if its excretory function is found to be somewhat impaired unilateral nephrectomy is not indicated as a treatment for the hypertension alone It should then be practiced only if it is considered advisable for the renal disease itself This is in complete agreement with the views of others If both kidneys are diseased then the excision of the more diseased organ for the purpose of alleviating the hyper tension is certainly not justifiable

We have found that in dogs constriction of the main artery of one kidney does not result in elevation of blood pressure if the ureter of the same kidney is occluded This would indicate that in human hypertension presumably on the basis of unilateral disease if the ureter of this kidney is completely obstructed there is some prob ability that the hypertension is not being caused by the involvement of this kidney and that the other kidney may be the cause as a result of disease without detectable disturbance of renal excretory func tion or that the hypertension has some other cause In such cases therefore the removal of the obviously diseased kidney should be undertaken only because of the other symptoms and not for the purpose of reducing the hypertension In a few cases of human hypertension however in which a completely hydronephrotic kid ney was removed the blood pressure promptly returned to normal and has remained normal for many months

As in the case of many discoveries in medicine there is likely to follow an exaggerated enthusiasm for any new procedure that offers a possible cure for a pathologic condition Unfortunately in some cases of hypertension one kidney has been removed when it was not fully established that the other kidney was normal This has resulted

not only in the failure of the blood pressure to fall but in some cases, even in an aggravation of the blood pressure renal failure and a fatal outcome To remove the more diseased of two diseased kidneys for the purpose of curing hypertension is certainly not justifiable

In animals with persistent hypertension due to bilateral renal ischemia the surgical production of collateral circulation to the ischemic kidney has also resulted in the return of the blood pressure to normal but the few attempts to do this to the kidney in human cases of hypertension have not yet been successful However up to the present time the attempt to produce collateral circulation has been practiced on only one kidney in hypertensive human beings in which both kidneys were presumably diseased The difference between the results in man and animals is due partly to this but it is undoubtedly also due to the fact that in the dog the intrarenal vessels are not organically diseased while in man in most instances it is the intrarenal and even preglomerular arterioles that are affected An anastomosis of extrarenal and intrarenal vessels could therefore prove of little or no value unless the ischemia were due only to disease of the larger intrarenal vessels or better to the extrarenal portion of the renal artery The occurrence of such cases in man has already been reported but the diagnosis in life is difficult

SUMMARY OF THE SIMILARITIES AND DIFFERENCES BETWEEN HUMAN ESSENTIAL AND EXPERIMENTAL HUMAN HYPERTENSION

In two excellent recent books on the subject of hypertension almost diametrically opposite views have been expressed about the mechanism of the elevation of the blood pressure Goldring and Chasis (2) concluded that the weight of the evidence was against the identity of the mechanism in human essential and experimental renal hypertension They postulated the existence of a primary humoral mechanism of unknown origin to which a renal component may contribute a secondary and accessory effect Braun Menendez and collaborators (4) including Dexter who translated the book into English have adopted the view that human essential hypertension in both its benign and malignant phases is of renal origin I believe as they do that experimental renal hypertension does faithfully reproduce human essential hypertension in most respects

In experimental renal hypertension as in human hypertension there may be no significant disturbance of renal excretory function — the benign phase or there may be pronounced renal excretory functional disturbance with uremia — the malignant phase depending entirely in experimental hypertension upon the degree of constriction of the main renal arteries An increase in the concentration of guanidine in the blood of animals and of man in the malignant phase of the hypertension has been demonstrated, but this has little or no significance with relation to the hypertension because it occurs also in bilaterally nephrectomized animals that have azotemia but no hypertension As in human hypertension so also in experimental renal hypertension cardiac action is increased but cardiac rate and output, volume viscosity and peripheral flow of blood and venous pressure remain unaltered Pulmonic arterial pressure remains unaltered, in both man and animals when the hypertension is uncomplicated by left ventricular failure as indicated by a normal right heart In the benign phase of hypertension in both man and animals cardiac hypertrophy develops affecting mainly the left ventricle and medial hypertrophy of the arterial vessels also occurs in both In the malig

nant phase in both there are in many organs the identical typical vascular lesions arteriolar necrosis fibrinoid degeneration and necrotizing arteriolitis

With few exceptions the response to medical therapeutic measures of great variety is the same in both human and experimental renal hypertension In both man and animals hypertension associated with unilateral renal disease may be cured by the excision of the diseased kidney provided the other kidney is normal Bilateral nephrectomy does not result in a rise of blood pressure in either man or animal I have personally observed one patient from the day when her only kidney was removed until death six days later without noting any elevation of blood pressure despite the rapidly developing profound azotemia Sympathectomy partial or extensive may result in at least a temporary fall of blood pressure in human hypertensives without affecting the primary cause of the hypertension but there is little or no effect as a result of this procedure in animals Whether this difference exists because the dog does not assume the orthostatic position with its consequent hemodynamic effects on the vasomotor apparatus cannot be stated with certainty at present The fact that after sympathectomy the blood pressure falls profoundly in some cases only when the patient is in the vertical position that it rises again when the horizontal position is assumed and that it returns to the original high level in a considerable percentage of the hypertensive patients favors the probability of a renal humoral mechanism in which the effect of the vasoconstrictor substance is presumed to act directly on the musculature of the peripheral arterioles and not by way of the vasomotor nerves This is in keeping with the conclusions of Prinzmetal and Wilson and of Pickering as a result of their studies of the pathogenesis of human hypertension

The frequent fall of blood pressure in the late stage of pregnancy in animals with experimental renal hypertension remains as unexplained as a similar fall which has been observed by obstetricians in some hypertensive pregnant women The observation of polydypsia and polyuria in rats with experimental renal hypertension has not been emphasized in human hypertension and has not been reported in hypertensive dogs although the diuretic effect of renin injected intravenously into dogs has been mentioned This deserves more investigation

Renal blood flow is reduced in most cases of hypertension in man and in experimental renal hypertension in animals The indirect studies of blood flow through the kidney in man do not demonstrate clearly the physiological effect of the sclerosis of the afferent arterioles because the presumable vasospasm of the efferent arterioles which *results in a high glomerular filtration fraction* tends to mask it Although the interference with afferent flow is definite in the animals and obviously brought about by the constriction of the main renal artery yet the same indirect signs of efferent vasospasm and high glomerular filtration fraction have been reported in the hypertensive animals *In both man and animals this similar effect may be* secondary to the primary humoral mechanism of renal origin which results from the hemodynamic disturbance produced by the preglomerular vascular disease and the constriction of the main renal artery respectively

The presence of renin has been demonstrated in the renal venous blood of ischemic kidneys of man and animals and an intravenous injection of renin or hypertensin also gives the indirect evidence of efferent vasospasm Renin has been demonstrated in the systemic blood of recently hypertensive dogs and in patients with hypertension due to acute glomerulonephritis yet the failure to demonstrate it in the systemic blood in benign human and in experimental renal hypertension may be only because the amount of blood used for the tests has *been inadequate or because of the lack of sensitivity of the method* for its detection Whether the humoral mechanism is effective in only the relatively acute stages of hypertension and whether as has been suggested there is in the later stages a greatly increased sensitivity to hypertensin remain to be determined These matters deserve much more study The comparative summary of the pharmacologic effects of renin and of the circulatory dynamics in hypertensive animals given in Table 3 shows that the parellelism is striking but this does not mean *that the chemical mediation of hypertension* by means of renin has been proved either for animal or man The participation of other pressor substances such as epinephrine tyramine pitressin and guanidin can be excluded from serious consideration The evidence for this has already been given

As in human hypertension so also in experimental renal hypertension the level of blood pressure tends to go higher in hypertensive animals that gain weight but it has not been proved that a high

protein diet or the ingestion of a large amount of urea increases the blood pressure in man or animal.

Although the elevated systolic blood pressure of hyperthyroidism in man is relieved by thyroidectomy, yet it is doubtful that any of the known endocrine organs play a primary part in either essential hypertension associated with vascular disease in man or in experimental renal hypertension in animals. There is no proof that the hypophysis plays a part in the pathogenesis of renal hypertension but there are definite indications that the adrenal cortical hormones do play a secondary part in the development and maintenance of experimental renal and perhaps of human hypertension. The adrenal cortex plays a part in influencing the production of hypertensinogen. This action is evidently exerted by an effect on the liver which is probably the source of this protein.

There are so many similarities between human essential hypertension associated with vascular disease and experimental renal hypertension that it does not seem unreasonable to suggest that the former may also be of renal origin. All of the more recent studies by Shorr and collaborators, by Shipley and Helmer, by Trueta and collaborators, by Selye and collaborators and by Hartroft still point directly to the central position occupied by the kidney in the pathogenesis of experimental and probably of human essential hypertension. Even if the renal origin of this form of renal hypertension should become established, it would still remain necessary to determine the cause of arterial and arteriolar sclerosis which, when it affects the kidneys to a sufficient degree, initiates the humoral mechanism of the hypertension. The failure of animals to develop widespread arterial and arteriolar sclerosis even after years of hypertension without accompanying impairment of renal excretory function (the benign phase) does not lend support to the view that hypertension is a sufficient condition for the determination of vascular sclerosis. It must be admitted, however, that this may mean only that the blood vessels of animals are less sensitive than human vessels to the effect of increased intravascular tension alone, although they appear to be even more sensitive to the conditions which determine the necrotizing vascular changes of the malignant phase of hypertension. Now that the probable primary significance of renal arterial and arteriolar sclerosis has been indicated by the experimental studies, the cause of the vascular disease has become the most important problem for in-

vestigation The recent contributions to this subject of Selye an collaborators and of Hartroft may prove to be a step in the righ direction

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INDEX

A

B

C

This Book

THE RENAL ORIGIN
of
HYPERTENSION

By HARRY GOLDBLATT M D C M

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